ANGLIA RUSKIN UNIVERSITY

THE ROLE OF POSTERIOR PARIETAL ACTIVITY IN MULTISENSORY INTEGRATION OF EPISODIC CONTEXTS

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ANGLIA RUSKIN UNIVERSITY ABSTRACT
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THE ROLE OF POSTERIOR PARIETAL ACTIVITY IN MULTISENSORY INTEGRATION OF EPISODIC CONTEXTS

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This thesis endeavoured to investigate the nature of the relationship of the posterior parietal cortex (PPC) with richness of episodic memory, and particularly binding of multisensory contexts in retrieved episodes. Electrophysiological signatures (ERPs) of memory retrieval were examined in order to determine the association of posterior parietal signals with increased recollection of multisensory episodic contexts.

In two studies of the Old/New recognition ERP measures the increased electrophysiological response over PPC sites was found to be significantly associated with the fine amount of multisensory details retrieved in an extended source memory paradigm. Parietal ERPs were shown to directly vary across 4 levels of increasing multisensory source memory performance. Subsequent examination of recognition ERPs over the PPC further specified that this was a recollection enhancement which was distinguished from similar familiarity-related signals.

In order to evaluate the causal influence of this PPC electrophysiological enhancement on retrieval, transcranial direct current stimulation (tDCS) was employed as a source of cortical neuromodulation. In two experiments tDCS was applied before participants performed source retrievals in the same source memory task significantly associated with enhanced PPC recollection –based activity. Anodal and cathodal tDCS to the PPC did not affect recognition performance, however anodal stimulation lead to an

enhancement in source memory performance above sham performance. Conversely, anodal stimulation of the M1 did lead to an enhancement of recognition accuracy, but no effect on source memory performance. Taken together, it can be concluded from these studies that PPC activity distinctly influences the integration of multi-sensory episodic details.

Keywords: episodic memory, posterior parietal cortex, electroencephalogram (EEG), neuromodulation, tDCS

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Chapter 1: General introduction: The neural system of episodic retrieval

Numerous regions throughout the brain have been implicated in the process of recollection, and among them the prefrontal cortex (PFC), regions of the medial temporal lobe (MTL), and the parietal area broadly referred to as the posterior parietal cortex (PPC) are consistently recruited, although the patterns of involvement may vary with task (e.g., Dobbins, Foley, Schacter & Wagner, 2002; Cohen & Eichenbaum, 1993; Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). The MTL is known to be involved in the initial encoding and representation of memories, and is consequently recruited in memory retrieval (Graham, Barense, & Lee, 2010). Dissociations among underlying processes have been identified, with the perirhinal cortex associated with the binding of visual (and possibly conceptual) object features, the parahippocampal cortex with representation of related spatial and temporal context (i.e., the 'where' and 'when') and the hippocampus responsible for binding the object-specific and contextual information into rich, coherent episodic representation (e.g., Bright, Moss, Longe, Stamatakis & Tyler, 2007; Eacott & Gaffan, 2005; Eichenbaum, Yonelinas, & Ranganath, 2007; Vilberg & Rugg, 2008).

Evidence for prefrontal (PFC) and parietal involvement has focused on their role in episodic recollection for detailed contextual features. The PFC has been associated with the initiation of top-down selection, maintenance, and updating of episodic features (Rugg, Fletcher, Chua, & Dolan, 1999). The region is also involved in evaluative retrieval processes during recollection, with sites of recruitment found to vary with overall level of engagement required by a given task (Badre, 2008; Bunge, 2004; Christoff & Gabrieli, 2000; Raposo, Han, & Dobbins, 2009; Wagner, 2002). Although the importance of MTL in learning and memory has long been recognised, the parietal cortex has been increasingly identified as fundamentally involved in the integration of episodic features. A posterior portion of the parietal cortex (PPC) comprising the angular and supramarginal gyri, intraparietal sulcus, precuneus, and often the temporal parietal junction has been found to support fine-grained

featural recollection, and its involvement has been closely associated with measures of successful retrieval (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008 Spaniol et al., 2009; Kim, 2010; Vilberg, & Rugg, 2008; Levy, 2012). This manifests as a selective sensitivity to strength and depth of encoding within memory tasks, and the contributions to retrieval distinguishing recollection (recovering contextual details) from familiarity (the feeling of 'oldness'), that in contrast does not differ in responses across cue (Shannon & Buckner, 2004) or item modalities (Duarte, Henson, &Graham, 2011), or reward contingencies (Han, Huettel, Raposso, Adcock, & Dobbins, 2010), but tends to be stronger in the left hemisphere (Guerin & Miller, 2009).

Increasingly convergent functional neuroimaging findings of episodic memory have implicated the PPC as a highly integrative site for recollection of multimodal features of an episode, supporting multiple sub-processes of episodic retrieval (Shimamura, 2011; Wagner,Shannon,Kahn, & Buckner, 2005). PPC subregions show strong connectivity with the default mode network regions (DMN), including the MTL, and are involved in engaging representations of episodes (Sestieri, Corbetta, Romani, & Shulman, 2011; Rissman, Chow, Reggente, & Wagner, 2016). It also provides critical nodes of activity with the fronto-parietal control network (FCPN) supporting the ongoing demands of transformation and manipulation of retrieved information for flexible use. Potential extension of these functions is to the accumulation of mnemonic information from regions across the PPC and the MTL for the evaluation of judgements of familiarity and other indicators of "oldness" (Sestieri et al., 2014*)*. Further research of the dynamic activity during memory retrieval has found that the integration of uni and bi-modal contexts of reinstated episodes can be specified to activity within this region (Richter, Cooper, Bays, and Simons, 2016; Yu, Johnson, & Rugg, 2012; Kuhl & Chun, 2014; Bonnici, Richter, Yazar, & Simons, 2016).

Despite the varied findings implicating the function of the PPC in episodic retrieval, a select few instances of episodic memory impairment in patients with PPC lesions have been reported, and this likely reflects that lesions are rarely restricted to areal boundaries, making the locus of the lesion hard to determine; patients are typically tested months or years post-lesion and likely have undergone functional reorganisation of the surrounding tissue; and

lesion retrieval deficits are challenged to be separated from encoding deficits (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Simons, Peers, Mazuz, Berryhill, & Olson 2010). Patient studies frequently report lowered confidence in episodic memory judgements (Ally, Simons, McKeever, Peers, & Budson, 2008; Haramati, Soroker, Dudai, & Levy, 2008; Hower, Wixted, Berryhill, & Olson, 2014), and decreased endorsement of vivid remembering (Davidson et al., 2008; Ciaramelli et al., 2017), though objective retrieval differences have been suggested particularly for bi-modal contexts (Ben-Zvi, Soroker, and Levy, 2015). Attempts at simulation of temporary lesions using non-invasive brain stimulation has similarly resulted in differences in source memory confidence (Yazar, Begström , and Simons, 2014; Chen et al., 2016), as well as uni and bi-modal source retrieval (Sestieri, Capotosto, Tosoni, Luca Romani, & Corbetta, 2013; Yazar, Bergström, & Simons, 2017).

Based on these findings it is proposed that the PPC acts as a convergence zone that binds multimodal episodic ensembles within the neocortex during episodic retrieval, akin to the first order convergent/divergent zones of recollective reinstatement predicted by Damasio (1989). This is supported by its neuroanatomical location linking occipital, temporal, and other parietal regions (Critchley, 1966), and dense connections with the dorsal and ventral visual pathways, the PFC, and the MTL have been established (Andersen, Asanuma, Essick, & Siegel, 1990). Consequently, it is optimally positioned to bind intermodal contextual features, and will be implicated in establishing relational links between spatially and temporally disparate multimodal contexts of an episode that are coactivated and maintained during recollection. Sparing, though increasing, findings have been able provide strong support for this role, and there remains a demand within the literature to demonstrate objective evidence implicating the PPC in multimodal retrieval that accounts for the continuous range and richness of contexts indicative of the vivid episodic experiencing that has been purported. In an attempt to address this need, this thesis examined the role of the PPC in episodic memory through characterisation of its activity during retrieval, and assessment of its causal influence on memory performance.

A memory task paradigm was employed throughout the thesis that tested source memory across three multimodal contexts (metacognitive, spatial, and auditory) that addressed

greater episodic richness than accounted in the previous bi-modal memory paradigms. Electrophysiological measures (ERPs) were selected to capture the subtle continuity of PPC function that is proposed, and a neurostimulation technique, transcranial direct current stimulation (tDCS), was subsequently used to modulate the observed PPC activity associated with task performance. It was predicted that increased richness of episodic retrieval would correlate with enhanced ERPs from PPC sites, and that direct excitation of the PPC with tDCS lead to greater source memory task performance, whereas inhibition of the PPC would reduce the task performance. The first two investigations concerned PPC activity during retrieval, and associated a known ERP component with increased success in retrieving multimodal sources in the episodic memory task, demonstrating this in the first experimental chapter and specifying this association to the PPC in the second. The last two investigations examined the causal nature of the PPC's activity during retrieval. The first of these identified a causal influence of PPC modulation with tDCS that was evident in one (anodal) experimental group, and was followed by an investigation of the role of individual differences in mediating the behavioural effects of tDCS to the PPC. A discussion chapter concludes the thesis. The next chapter will introduce and consider the methods and design used in the thesis.

Chapter 2: Experimental Methods

Retrieval Task Design

In order to investigate the sensitivity of the PPC to richness of episodic retrieval, a source memory task was employed across three studies. The task aimed to elucidate differences in retrieval of increasingly multi-sensory contexts of episodes. In order to identify fine-grained sensitivity the task employed 4 retrieval sources in order to provide a more continuous scaling of retrieval quality and accuracy than typically examined in memory context retrieval paradigms (Wilding, 1999). Additionally, this task feature provides more objective measures of memory retrieval across a broader range than that of previous examinations of graded indexes of retrieval (Wilding, 2000, Richter et al, 2016).

Stimuli

The same stimuli were employed across all studies. In an adaption of a study by Bergstrom et al., which associated the late posterior parietal ERP signatures with source accuracy effects arising from the medial parietal cortex, faces were selected as visual item stimuli in order to maximise recollection accuracy (2013). Further to this, famous faces were included, among other nonfamous faces. Famous face stimuli were compiled from 48 male and 48 female celebrity photos matched by gender for rated age, ethnicity, and decade of fame. Pilot familiarity ratings from a sample of 15 participants identified the 40 most familiar male and female faces that surpassed an average rating threshold of 4 on five point liker scale of familiarity, which were included in the task. These faces were matched for age, ethnicity, and gender with 240 nonfamous faces from the Glasgow Unfamiliar Face Database (Burton, White & McNeil, 2010) to compile an item stimuli set of 320 black and white photographs of faces. This included The 80 famous and 80 nonfamous faces shown during study and test phases, and 160 nonfamous faces only shown during test phases. Four audio recordings were used as auditory stimuli in the study phases. The recordings featured a female or male speaker asking the question either “Is this face pleasant?” or “Is this face a celebrity?”, and lasting an average ~1sec. Stimuli were presented using Eprime software on a 17” high-

resolution LCD monitor with a refresh rate of 60Hz, with participants seated 60cm away during electroencephalogram (EEG) recording, and face stimuli subtended a 6-degree angle.

Task

The source memory task consisted of two phases, a study and a test phase, and participants completed five blocks of study-test cycles in the EEG studies, and 4 blocks in the tDCS studies. On study phase trials participants voluntarily encoded study items and three item contexts in trials by responding to 3 questions for a given item. In each trial they were presented with a fixation cross at the centre of the screen for 100ms. Then a famous personality or a nonfamous face was presented to either the left or right side parallel to the fixation cross for 1000ms, and they were asked a question over headphones to perform one of two tasks. In the pleasantness task participants were asked to indicate if the face was pleasant or not. In the celebrity task they were asked to indicate if the face was of a celebrity or not (yes or no). This was followed by a second screen with instructions to indicate on which side the face was shown, (left or right), and a third screen with instructions to indicate the gender of the voice that gave the task question, each preceded by presentation of a fixation cross for 100ms. Participants received on-screen instructions to indicate a choice by pressing the “c”, or the “m” key on the keyboard as quickly as possible. Following the Bergstrom et al. study (2013) which similarly tested source memory for faces, participants were given up to a maximum of 2400ms to respond to each memory judgement. In an initial pilot of the task with shorter response windows, participants failed to achieve accuracy rates in each of the retrieval categories above %50, so this time was adopted to allow for sufficient accurate responses within trials to examine source accuracy differences. Each study phase lasted 32 trials with 16 famous and 16 nonfamous faces, matching the study list length of earlier studies examining the association of posterior parietal signals with graded recollection (Wilding, 1999, 2000). Following completion of the study phase participants received instructions for the test phase.

In the test phase participants saw all 32 faces from the study phase, as well as 32 new nonfamous faces not previously encountered, and they were tested on their source memory for the studied faces. On test trials participants first were presented with a fixation cross at the centre of the screen for 100ms, followed by a face for another 1000ms, which they were instructed on screen to indicate whether it had been previously presented at study ("old" or "new"), for a maximum of 2400ms. This was then followed by a second on-screen instruction to indicate which rating task they had completed for the given face, a third to indicate on which side the face was shown, and a fourth to indicate the gender of the questioner, each for a maximum of 2400ms, and preceded by presentation of a fixation cross for 100ms. On trials for which a new face was presented participants could press any key to respond for the three subsequent indications. The test phase lasted 64 trials, and concluded the block, after which participants had the option to take a break before beginning the next block, as shown in Figure 1.

The study phase was equally balanced for amount of famous and nonfamous faces presented, the frequency of the celebrity and pleasantness rating tasks, the male and female voices delivering the task question, and the location of the image on the left and right side. All trials were counterbalanced across these four factors across blocks, and were randomized for order of presentation. Each block lasted for ~9min short breaks between each block. Assignment of face stimuli was counterbalanced across the different study conditions, and matched to distribution of stimuli characteristics used at test. No repetition of face stimuli occurred between blocks.

Participants

Thirty participants (19 female, aged 18 to 42, mean = 25 years) in the EEG, and 50 participants (29 female, aged 19 to 39, mean = 23 years) in the tDCS study completed the previously described source memory task testing for multimodal retrieval. Each was either paid at a rate of £7/hour, or received credit towards fulfilment of an experimental participation requirement for their course. All participants were right-handed, had no history of neurological or psychiatric disturbances. TDCS participants did not meet any criteria of

contraindications for safe use of tDCS (Nitsche, 2008). These criteria include history of drug abuse, fainting, or migraines, pregnancy, being a licensed HGV driver, or having any metallic implant in the neck, head or eye, or any other implanted electrical device. All Participants provided written informed consent in a manner approved by the local department ethics. They were divided into two groups, with 15 participants in the anodal group, which received active anodal tDCS and sham stimulation, and 15 participants in the cathodal group, which received active cathodal tDCS and sham stimulation completed the previously used source memory task testing for multimodal retrieval

EEG recording and data analysis

An EEG recording measures the voltage change over time as a result of the summed electrical activity of large populations of neurons which is conducted through the brain and skull to the scalp. During an EEG experiment, when trial recordings are time-locked to an event of interest (e.g. stimulus presentation) and averaged, the derived measures of change in the voltage amplitude of the EEG signal are referred to as Event-Related Potentials (ERPs). Time-locking trials to an event allows the neural activity preceding, during, and after stimulus presentation to be investigated. However, accurate interpretation of the resulting ERPs requires careful appreciation of the underpinnings of the electrical activity from which they are derived (Luck, 2014; Picton et al., 2000).

The signal recorded at the scalp reflects changes in membrane potentials of neurons as large populations are activated. At rest, the interior of a neuronal cell is negatively charged relative to the exterior. When the cell becomes active, ion channels in the membrane open, allowing the ions outside the cell to enter. Consequently, the inside of cell becomes positively charged with respect to the outside (depolarised), initiating an action potential. The resulting signal then travels down the neuronal axon to the terminal at the synapse. Communication between neurons occurs when neurotransmitter molecules are expelled from one neuron into a synapse and reach the next neuron via diffusion. Reception of these neurotransmitter molecules triggers an influx of positively charged ions in the post-synaptic neuron, leading to a post-synaptic potential. It is this change in chemical potential that is

measured by the EEG, however detection of such voltage changes requires synchronous firing of large populations of neurons. Moreover, these cells need to be spatially aligned such that neurons with opposing positive and negative dipoles do not nullify the observed potentials. Consequently each electrode on the scalp measures the sum of the current flow that is directed underneath it, which may arise from several sources within the cortex. As a result, the activity recorded at the scalp will only reflect a small proportion of the total activity within the cortex due to the activity of neurons that may counteract each other, or may not be arranged in the optimal orientation (Makeig, 2016). Source localisation methods have highlighted that no more than 30% of the variance recorded at one electrode is produced by a single source (Makeig & Miyakoshi, 2015). Moreover, due to the nature of volume conduction, changes at one source will likely be detected by several neighbouring electrodes.

For the ERP studies EEG was recorded via 2 32-channel DC amplifiers using Brainvision Recorder and ActiCap software (Brain Products, Munich, Germany). For each participant 60 electrodes were mounted on a cap while two additional ocular electrodes were placed on either side of the face to monitor horizontal eye movements, and two above and below the left eye to monitor vertical eye movements. Electrode impedances were kept under 5 kΩ when possible but were accepted when below 20 kΩ and the sampling acquisition rate was 2000 Hz. The position FCz was the reference electrode during acquisition; TP9 and TP10 were used as references during the analysis.

Using Brainvision Analyser Version 2.0. (Brain Products, Munich, Germany), trials contaminated with eye movements and other artefacts were rejected. Following a 0.03 to 70Hz band pass filter and 50Hz notch filter to remove electrical noise on the raw data, as was similarly employed by Wilding (2000) in their ERP investigation of a dual context source memory paradigm, the data were processed through an ICA within the Brainvsion Analyser software which identified and corrected for ocular/motion components. The ocular correction ICA first employed Mean Slope algorithm of Gratton et al. (1983) that detected any high-amplitude activity in the scanned channels, and these data labels were used in a

decomposition of the whole data set with the Infomax ICA procedure (Bell and Sejnowski 1995). The extracted components were evaluated and removed according to the Relative VEOG/HEOG Variance, at thresholds of %10. For each participant segmentations were made based on markers for the onset of each face presented on a test trial, and baseline corrections were carried out 100ms before stimulus onset before the average was obtained for each condition. ERPs were collected for 1000ms post stimulus, and averaged within categories of 0, 1, 2, or 3 correct responses to source memory judgements for a given study trial.

Transcranial direct current stimulation protocol

Transcranial electrical current stimulation is a form of non-invasive brain stimulation in which weak electrical current is passed through two or more electrodes that are placed on the scalp or other sites, such as the leg or arm. Due to the direction of the flow of the electrical current, transcranial electrical current stimulation is mainly categorised into two types: transcranial alternative current stimulation (tACS) and transcranial direct current stimulation (tDCS), which is employed in later studies. Electrodes in this type of stimulation are called anode (positive electrode) and cathode (negative electrode) and current flows from anode to cathode. Deployment of tDCS is referred to as anodal or cathodal according to the electrode which is placed over the target site of stimulation. For example in anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC), the anode electrode would be placed over the left DLPFC and the cathode electrode would be placed somewhere distant, often over the contralateral supraorbital area. Whereas cathodal stimulation suppresses cortical excitability, anodal tDCS is seen to enhance cortical activity and subsequently improve behavioural patterns (Galea, et al., 2009; Miranda, et al., 2006; Nitsche, et al., 2003).

For decades electrical brain stimulation has been used in clinical and cognitive applications, but recently researchers have studied and developed new applications for this method. As summarised by Nitsche et al. (2008), since 1998 it has been shown that transcranial electrical brain stimulation can be effective for different perceptual, cognitive and behavioural functions such as short term memory and motor learning, as well as for clinical applications,

such as the treatment of migraine and stroke. The mechanisms of action of tDCS are studied in many ways but are yet to be clarified.

Evidence that tDCS can induce lasting changes in spontaneous neuronal activity, without directly inducing action potentials during the period of stimulation, may account for intra-stimulation effects on cognitive and behavioural function. Wagner and colleagues (2007) used computer simulation to demonstrate that current densities between 0.77 and 2.00mA/cm2 are well below the action potential threshold for cortical neurons (Tehovnik, 1996; T. Wagner, Valero-Cabre, et al., 2007). Although current densities below 2mA/cm2 may not directly produce action potentials, previous animal studies indicated that even these amounts of electrical current can change the firing rate of neurons. Bindman et al. (1964) found that anodal direct current stimulation increases, whereas cathodal direct current stimulation decreases spontaneous neuronal firing in vivo.

Purpura and McMurtry (1965), further demonstrated non-synaptic mechanisms of tDCS, finding that 30-400 μA/mm2 anodal stimulation caused neuronal depolarisation and under equal cathodal stimulation caused hyperpolarisation, as measured from intracellular recordings. Similar evidence of post-synaptic changes in resting membrane potential was observed in humans. Using transcutaneous electrical stimulation to control for cortical input, Ardonlino et al. (2005) demonstrated that 10 min 1.5mA cathodal tDCS to the motor cortex reduced the amplitude of recorded motor evoked potentials (MEP) from peripheral muscles. Synaptic mechanisms have also been found to contribute to the effects of tDCS, as cathodal tDCS was shown to induce long-term depression of synaptic transmission (LTD) through reduced pre-synaptic discharge and post-synaptic hyperpolarisation (Nitsche, et al., 2003). Additionally the modulation of glutamate, NMDA, AMPA, and GABA receptors (Nitsche et al., 2004), extracellular calcium (Hardingham et al., 2006), and protein synthesis (Cooke & Bliss, 2006) are found to be neuroplastic mediators of the effects of tDCS.

The efficacy of tDCS to induce effective modifications depends on several factors such as current density, which is the quotient of current strength and electrode size (Purpura & McMurtry, 1965), electrode montage, duration of stimulation and phase of stimulation.

Correct placement of the electrodes is important to achieve effective stimulation of desired brain areas, and different effective combinations may modulate different neuronal populations. In typical electrode montages the positive electrode (anode, red colour) is placed over the target area and the negative electrode (cathode, blue colour) is positioned so that the resulting current flow allows effective modulation of neuronal activity under the anode. For example Nitsche et al. (2008), and Im et al. (2008) suggest that to modulate the left dorsolateral prefrontal cortex the target electrode would be placed over F3 (according to the 10-20 international system). The suggested location of the reference electrode would then be the contralateral right supraorbital area.

A cephalic reference electrode may also stimulate the brain area beneath it as this electrode is not physiologically inert. Since both electrodes (target and reference electrodes) have similar current and both are placed on the scalp, there is the possibility that both brain areas are stimulated (Datta et al., 2009; Dmochowski et al., 2011; Bikson & Rahman, 2013; Knoch et al., 2007). There are some methods to reduce the stimulating effect of the reference electrode, for example using bigger reference electrodes to reduce the current density (Fregni, et al., 2008). Another example is placing the reference electrode on the periphery such as the shoulders (Accornero, Li Voti, La Riccia, & Gregori, 2007; Ferrucci, Marceglia, et al., 2008).

The focality of tDCS is mostly limited to the size of the electrodes. Because of the typically large electrode size (5cm by 5cm), tDCS might stimulate cortical areas adjacent to the targeted area (Gandiga, Hummel, & Cohen, 2006). Focality can be increased by reducing the electrode size, however small electrodes could have qualitatively different effects due to shunting of current in the scalp, greater edge-effect relative to the overall electrode area, and some other factors (Roth, 1994; Wagner, et al., 2007). Using computer simulation, Wagner et al. (2007) revealed that the overall percentage of electrical current affecting the cortex and deeper area was small. The shunting (i.e., the flow of current along the scalp surface as opposed to the cortex) effects modelled were considerably greater for the 1 cm^2 electrodes compared to the larger electrodes. They found this indicative of an inverse relationship of electrode size and shunting due to the varied resistive paths of current flow.

It has been shown that larger current densities induce stronger effects of tDCS. Furthermore, it is necessary to apply enough current strength to have detectable effects (Nitsche & Paulus, 2000; Boggio, et al., 2006; Fregni, et al., 2005; Iyer, et al., 2005). However Priori et al. (1998) found that weaker 0.3 mA anodal stimulation of the motor cortex actually reduces MEP size, suggesting that the direction of change may be highly amplitude dependant. It was further shown in the motor cortex that when stimulation intensity is increased from 1 mA to 2 mA, direct current loses its opposing polarities, which results in cathodal stimulation inducing excitatory effects (Batsikadze et al., 2013).

The residual effects of tDCS are also heavily dependent on the duration of stimulation (Nitsche, et al., 2003; Nitsche & Paulus, 2001). Nitsche and Paulus (2000) demonstrated that a short duration stimulation of primary motor cortex has short-lasting effects on motor cortical excitability which do not outlast the duration of stimulation itself. These short-lived effects, which do not last beyond stimulation, are called intra-tDCS, or online effects (Nitsche, et al., 2008). Across a series of studies on the motor cortex Nitsche and colleagues demonstrated that the physiological effects of tDCS last longer for stimulation durations of more than a few seconds (Nitsche, et al., 2003; Nitsche & Paulus, 2000, 2001). They found that the effect of 9 minutes of stimulation could last for up to 30 minutes and the effect of 11 minutes of stimulation could last an hour post-stimulation.

The effects of tDCS are also found to depend on the state of excitation of the brain tissue being targeted (Antal, Terney, Poreisz, & Paulus. 2007). Benwell et al. (2015) demonstrated that the degree of task-relevant neuronal pooling at the time of stimulation modulated the effect of tDCS, indicating that the populations of neurons affected by tDCS depends on how active they are during stimulation. Behaviourally relevant changes of neural activity reflect a shift in the balance between activity of task-relevant and task-irrelevant neurons, or signal-to-noise ratio, and tDCS consequently mediates this shift through preferential up-regulation, or down-regulation of active neurons contributing either ‘signal’ or ‘noise’ (Bikson and Rahman, 2013).

A CE-certified tDCS medical device was used in the current tDCS studies with a small battery-driven constant current stimulator (BrainSTIM Transcranial Stimulator, EMS medical, UK). The stimulator consisted of a stimulator machine and a pair of conductive rubber electrodes (5cm X 5cm) inside two saline-soaked sponges that were secured on to the skin. One electrode was placed on the P3 site of the International 10-20 System for EEG electrode placement (Jasper, 1958) to stimulate the left posterior parietal cortex and the other on the right cheek to serve as the reference (Jones & Berryhill, 2012; Tseng et al., 2012) , as seen to be estimated in Figure 2. The selected P3 site was identified from the earlier ERP findings, as activity coarsely specified over this region was found to be most responsive to successful source memory in the left hemisphere, though it has also been the preferred hemisphere for unilateral stimulation of the PPC in memory investigation (Chua et al, 2006). In the active stimulation blocks, a constant current of 1.5 mA began at the onset of the study phase for each block. Given the state-dependency of tDCS mediated effects (Benwell et al., 2015), stimulation was applied throughout the study task as it closely resembled the final retrieval task, and this would ensure that neuronal populations relevant to the retrieval process would be active and engaged by tDCS. Stimulation persisted for 4 minutes after the last study trial, lasting for a total of 10 min for each block. In the sham condition, the electrodes were also kept in place for the 10-minute interval but the current was applied only for the first 30 seconds. The fade-in and fade-out durations were 15 seconds for active and sham stimulation conditions. The stimulation intensity and duration was used which matched previous studies which used tDCS in similar investigations of the PPC in memory (Chen et al., 2014 & 2016). Once stimulation had been completed participants began the 10 min test phase.

The stimulation alternated between active and sham stimulation type between blocks (two blocks each), for a total of 40 min, comprising 20 min sham stimulation, and 20 min active stimulation, with 10 min between each stimulation, and a total of 30 min between each active stimulation. This block structure was employed to allow the effects of stimulation to dissipate after each test phase, as previous tDCS studies indicated that the effects of 10 min of stimulation to the PPC on memory retrieval do not last beyond 20 min (Pergolizzi & Chua,

2015). The stimulation alternated between active and sham stimulation type between blocks with constant electrode placement throughout the experiment, according to the current polarity participant group.

Safety of tDCS depends on both current density and stimulation strength (Nitsche et al., 2003). The current density induced by the tDCS protocol in the present study was a maximum of 0.0428 mA/cm2, which was well below the safety value of 25 mA/cm2 (McCreery et al., 1990). In regard to the stimulation strength, the total charge was 0.0056 C/cm2. This value was also far below 216 C/cm2, which has been found to have no significant heating effect at the electrode site (Nitsche & Paulus, 2000), or evidence of any neuronal damage (Nitsche & Paulus, 2001; Nitsche et al., 2003). It has been shown that tDCS neither causes epileptic seizures nor reduces the seizure threshold in animals (Liebetanz et al., 2006), thus seizures do not appear to be a risk for healthy participants. However, this might not hold for patients with epilepsy or a history of seizures. The tDCS protocol used in the tDCS experiment was therefore in accordance with the literature and safe for the participants. Debriefing and questionnaires following the study verified that participants had not experienced any discomfort or irritation from tDCS. The experiments were approved by the local ethical committee.

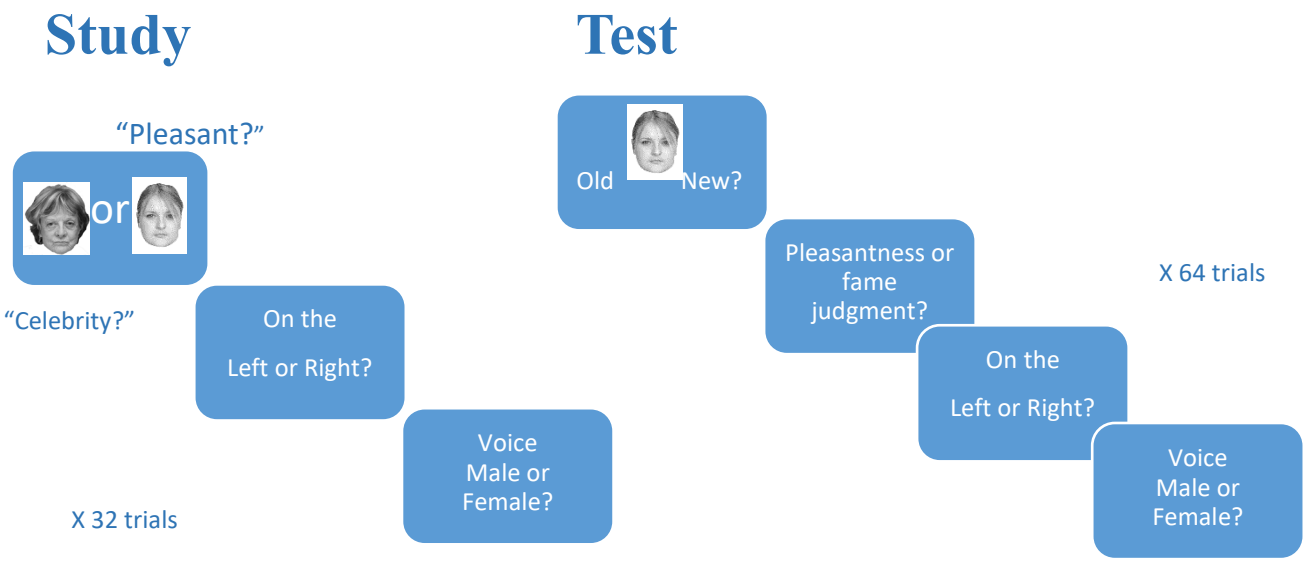

Figure 1. Source memory task structure for study and test phases

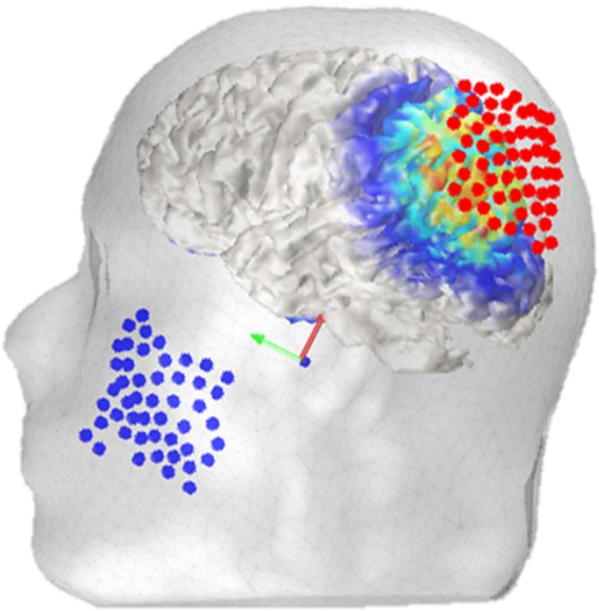

Figure 2. Modelled estimation of electrical current density for the tDCS electrode placement at P3 site and right cheek

Chapter 3: Neural Correlates of multimodal episodic retrieval

Converging functional neuroimaging research on episodic memory implicates the PPC as a highly integrative site for recollection of multi-sensory features in an episode (Shimamura, 2011), and a select few instances of episodic memory impairment in patients with PPC lesions have been reported (Ciaramelli et al., 2017; Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Simons, Peers, Mazuz, Berryhill, & Olson, 2010; Hower et al., 2014; Ben-Zvi, Soroker, and Levy, 2015). Thus, the PPC is implicated in establishing relational links between spatially and temporally disparate multimodal features of an episode that are coactivated and maintained during recollection. A central reason behind this proposed association is that the PPC is situated as a convergence zone linking occipital, temporal, and parietal cortices and dense connections with the dorsal and ventral visual pathways, the PFC, and the MTL have been established (Andersen, Asanuma, Essick, & Siegel, 1990).

Although it has been increasingly implicated in memory retrieval, few studies have examined the role of the PPC in the detail and multisensory richness of episodic retrieval. The present study seeks to address this need and examines the PPC electrophysiological response for successful retrieval of multimodal episodic contexts.

The application of scalp electrophysiology is frequently used to identify the human neural activity underlying information processing in cognitive neuroscience studies. One way to detect the neural activity underpinning cognitive function is to measure electrophysiological signalling in the brain. When a large group of neurons are activated together, the sum of the post-synaptic potentials of these neurons is measurable. The variation in the electrical potentials over the human scalp at a given time constitute the electroencephalogram (EEG). Event-related potentials (ERPs) are signals extracted from epochs of an EEG and are associated with specific stimuli or events. An ERP is suitable for providing information about the time course of cognitive processing because of its high temporal resolution, within the millisecond range.

Due to the high temporal resolution, EEG provides precise measures of the temporal characteristics of neural activities. A large number of studies have employed EEG to

investigate the correspondence between electrophysiological changes and underpinnings of memory retrieval by examining ERPs at retrieval (e.g., Smith, 1993; Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996; Wilding, 2000; Vilberg, Moosavi, & Rugg, 2006; Woodruff et al; 2006). In order to investigate the processes underlying episodic retrieval, these studies examined the differences between the ERPs in response to recognized previously studied items (Hits) and those for correctly rejected unstudied items (CRs). An "old/new effect" is revealed in the difference in the ERPs of Hits compare to CRs over the left lateral parietal cortex, also called the "left-parietal old/new effect" or the "successful retrieval effect" (Smith, 1993; Wilding Doyle, & Rugg, 1995; Wilding & Rugg, 1996). A more positive ERP for Hit responses than CR responses is typically observed, with an onset around 400ms post-stimulus and a duration of 400-600ms.

The left parietal old/new effect is considered to reflect the recollection rather than familiarity in recognition memory (Vilberg & Rugg, 2009a). Consistent with the claim that remember responses represent conscious recollective experience, Dűzel and colleagues found a left parietal old/new effect associated with remember, but not know judgments, of both studied items and unstudied lure items (1997). Another similar finding came from Smith (1993), who reported that, although the left parietal old/new effect was observed in both remember and know responses, the effect was significantly larger for remember responses than know responses. The findings of Schloerscheidt and Rugg (1997) also demonstrated that the left parietal old/new effect was observed across different modalities, whether by using lexical or pictorial stimuli.

Source memory studies also provide strong evidence about the association between the left parietal effect and recollection. The presence or absence of contextual information is claimed to distinguish between recollection and familiarity (Johnson, Hashtroudi, Lindsay, 1993). That is, contextual information is available in recollection but not familiarity. For such cases, accurate source judgments are used to identify when recollection takes place, though it is noted that some cases where the probed source cannot be retrieved, other non-criterial contextual information might be available to participants, thus source failures may not represent absence of recollection (Mulligan & Hirshman, 1997; Yonelinas & Jacoby, 1996).

Several studies were conducted to investigate whether the old/new effect is sensitive to source accuracy. For instance, in the study of Wilding and Rugg (1996), participants made old/new judgments followed by subsequent forced-choice source judgments. The results indicated a larger left parietal old/new effect for source-correct trials than source-incorrect trials. A more elaborate manipulation demonstrated that this effect is also sensitive to the amount of retrieved information, and the strength of recollection is graded (Wilding, 2000).

In general, it is agreed that the parietal old/new effect is an electrophysiological correlate of recollection based recognition, and the topography of this effect is thought to reflect left parietal lobe related activities. However, given the low spatial resolution and the inverse problem of EEG/ERP signals, it is difficult to demonstrate that LPPC is involved in recollection or recognition memory based on the ERP studies. Apart from ERPs, fMRI has provided refined spatial resolution and findings of extended LPPC activations in recognition memory. Recent work employing multi-modal neuro-imaging, which combined fMRI, EEG, and MEG in a source memory task, however, provided support that the spatial localization of this effect for source recollection arose from the medial PPC activation (Bergstrom et al., 2013).

We propose that the PPC functions closely with the MTL in integrating episodic features together into an ensemble and that episodic recollection will rely more on bindings within the PPC when the stimulus or event features to be retrieved are multimodal, and more on those of specified MTL regions when those features are closely within the same modality. Consequently, the more sensory-rich the recollection, the stronger the association the PPC will have with recollective responses, higher confidence of memory, and successful source memory. In a study addressing successful retrieval of multimodal episodic contexts, we recorded ERPs for performance on a multi-sensory source memory task. We predicted there would be increased amplitudes in the measured old/new effect with increased multi-sensory detail of retrieved episodes.

Method

Participants

Thirty participants (19 female, aged 19 to 39, mean = 23 years, SD = 4.87) completed a source memory task testing for the audio, visual, and metacognitive contexts of an episode, while undergoing EEG recording. Each was either paid at a rate of £7/hour, or received credit towards fulfilment of an experimental participation requirement for their course. All participants were right-handed, and had no history of neurological or psychiatric disturbances. Participants provided written informed consent in a manner approved by the local department ethics panel.

Stimuli

Three hundred and twenty black and white photographs of faces (80 of famous celebrities, 240 from the Glasgow Unfamiliar Face Database (Burton, White & McNeil, 2010)) were used for the visual stimuli. The 80 famous and 80 nonfamous faces shown during study phases were matched in proportion on age, gender, and ethnicity, as were the 160 nonfamous faces only shown during test phases. Presentation order of faces was randomised between participants. Four audio recordings were used for auditory stimuli, one of each task question spoken by a male, and one of each task question spoken by a female.

Procedure

The source memory task consisted of two phases, a study and a test phase, and participants completed five blocks of study-test cycles while undergoing EEG recording. On study phase trials participants were presented with a fixation cross at the centre of the screen for 1000ms. Then a famous personality or an nonfamous face was presented to either the left or right side parallel to the fixation cross for 1000ms, and they were asked a 2000ms auditory question over headphones to perform one of two tasks. In the pleasantness task participants were asked to indicate if the face was pleasant or not. In the celebrity task they were asked to indicate if the face was of a celebrity or not. This was followed by a second screen with instructions to indicate on which side the face was shown, and a third to indicate the gender of the questioner, both preceded by presentation of a fixation cross for 100ms. They received on-screen instructions to indicate a choice by pressing the “c”, or the “m” key on the keyboard as quickly as possible up to a maximum of 2400ms. Each study phase lasted 32

trials, and after one had been completed participants then received instructions to begin the test phase.

In the test phase participants saw all faces from the study phase, as well as 32 new nonfamous faces not previously shown, and they were tested on their source memory for studied faces. On test trials participants first were presented with a fixation cross at the centre of the screen for 100ms, followed by a face for another 1000ms, which they were instructed on screen to indicate whether it had been previously presented at study ("old" or "new"), for a maximum of 2400ms. This was then followed by a second on-screen instruction to indicate which rating task they had completed for the given face, a third to indicate on which side the face was shown, and a fourth to indicate the gender of the questioner, each for a maximum of 2400ms, and preceded by presentation of a fixation cross for 100ms. On trials for which a new face was presented participants could press any key to respond for the last three indications. The test phase lasted 64 trials, and concluded the block, after which participants had the option to take a break before beginning the next block.

The study phase was equally balanced for amount of famous and nonfamous faces presented, the frequency of the celebrity and pleasantness rating tasks, the male and female voices delivering the task question, and the location of the image on the left and right side. All trials were counterbalanced across these four factors and randomized for order of presentation. Each block lasted for ~9min for a total task time of ~45min with short breaks between each block. Assignment of face stimuli was counterbalanced across the different study conditions, according to stimuli characteristics, which were equally distributed with those used at test. No repetition of face stimuli occurred between blocks.

EEG recording and data analysis

EEG was recorded via 2 32-channel DC amplifiers using Brainvision Recorder and ActiCap software (Brain Products, Munich, Germany). For each participant 60 electrodes were mounted on a cap while two additional ocular electrodes were placed on either side of the face to monitor horizontal eye movements, and two above and below the left eye to monitor vertical eye movements. Electrode impedances were kept under 5 kΩ when possible but

were accepted when below 20 kΩ and the sampling acquisition rate was 2000 Hz. The position FCz was the reference electrode during acquisition; TP9 and TP10 were used as references during the analysis.

Using Brainvision Analyser Version 2.0. (Brain Products, Munich, Germany), trials contaminated with eye movements and other artefacts were rejected. Following a 0.03 to 70Hz band pass filter and 50Hz notch filter to remove electrical noise on the raw data, the data were processed through an ICA which identified and corrected for ocular/motion components. For each participant segmentations were made based on markers for the onset of each face presented on a test trial, and baseline corrections were carried out 100ms before stimulus onset before the average was obtained for each condition. ERPs were collected for 1000ms post stimulus, and averaged within categories of 0, 1, 2, or 3 correct responses to source memory judgements for a given study trial.

Results

Task data

Recognition of faces was high overall, with an accuracy of 0.81(MSE =0.09). Discrimination P (hit) - P (false alarm) was reliably above chance t(16)> 9.53, p <.001. Accuracy of source retrievals differed between modalities, F(2,28) =18.94, p <.001, with accuracy for face location being the highest at 0.66 (.011) accuracy for task the second highest at 0.63 (.011), though not significantly different from location (t(16)= -1.72, p =.261), and accuracy for voice the least at 0.53 (0.48), which differed from accuracy for location (t(16)= -8.55, p <.001) and task (t(16)= -6.82, p <.001). Reaction time (RT) for correct judgements overall, 1186ms (227), was faster than for incorrect judgements, 1446ms (308), $F(1,28) = 44.82$, $p < .001$. The RTs for recognition decreased when there were 0 source retrievals (950 ms (281)), 1 correct source retrieval (966ms (33)), 2 correct source retrievals (909ms (26)), (1206ms (270)), and 3 source retrievals (900ms (36)), however these weren't reliable differences, $F(3,16) = 0.849$, $p > .4$.

ERP Data

ERPs were formed from item recognition trials for which participants made 0, 1, 2, or 3 correct source retrievals for either of the task, voice gender, or location contexts successfully, or correctly rejected new items at test. Participants were excluded if they had insufficient (14 or less) trials to form ERPs in any of the categories, for a total of 17. The grand average ERPs for of all of the successfully recognition trials manifested a sustained positivity arising ~150-500 ms, with maximal amplitudes over left and right anterior and posterior sites (Figure 3.). In order to identify sites that displayed the largest old/new recollection effect the differences between the peak amplitude of ERPs for correctly recognized old items and ERPs for correctly rejected new times within a 200-400ms epoch post stimulus was calculated. Four electrode pairs from the left and right hemisphere exhibiting the maximal difference in the Old/New posterior component were selected for further investigation (see Figure 4 for an example electrode pair): Cp1 and Cp2, P1 and P2, P3 and P4, and P5 and P6 electrodes, paired on the left and right, respectively. The mean ERP amplitudes over the 200-400 epoch were calculated for the four source retrieval accuracy categories and paired comparisons across category were performed to examine the predicted magnitude differences, as well as to examine hemispheric differences.

Pairwise contrasts revealed significant effects of correct source retrieval context (3-correct vs. 2-correct: $F(1, 66) = 9.77$, $p<.01$; 2-correct vs. 1 correct: $F(1,62) = 15.54$, $P<0.001$: 1-correct vs. 0-correct: $F(1, 62) = 24.93$, $p <.001$). As can be observed in Figure 5, ERPs increased with accuracy of source memory for the trials. In a subsequent ANOVA for correct source retrieval that included hemisphere as a factor the main effect of source ($F(3,14) =8.82$, $p <0.01$) was accompanied by an interaction, due to greater increase in amplitude for right hemisphere electrodes ($F(3,14) =29.91$, $p <0.001$), with no main effect of hemisphere ($F(1,16) =1.50$, $p =0.238$).

Discussion

The ERP results indicate that the contextual richness of episodic retrieval increased with the strength of an early Old/New effect arising from posterior parietal sites, an onset which was remarkably early, but has been noted in previous similar investigations (Vilberg, Moosavi

and Rugg, 2006; Duarte et al., 2004; Tsivilis et al., 2001). Consequently, our present findings support those of others that the PPC is closely linked to the strength of episodic retrieval. Moreover, these PPC correlates integrated the retrieval of varied multisensory contexts from episodic memory.

Although the posterior parietal activity has been found to be highly associated with memory retrieval, a sparing few studies have directly implicated its function more extantly in the quality of memory retrieval. Patients with lesions to this area demonstrate only a lower confidence in the integrity of retrieved episodic contexts, which appears to reflect a reduction in the quality of the retrieved episodes, but not explicit impairments in retrieval (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Simons, Peers, Mazuz, Berryhill, & Olson 2010). Such findings implicate this region in retrieval, yet are insufficient to specify a role in binding of features. Non-invasive measures of PPC activity which have been found to be linked to episodic retrieval have predominantly been found for unimodal retrieval of visual or auditory features (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Vilberg & Rugg, 2008). Consequently our findings are among the first to provide support for this region's proposed role in the integration of the multimodal episodic retrieval.

Moreover, associations of the PPC with in vivo measures, when demonstrated directly with retrieval performance, have not employed measures along the graded continuum of successful performance which is anticipated to occur in retrieval of features within an episode (Wilding, 2000). Rather, these associations have been made with discrete measurements of episodic retrieval, such as the retrieval success, or failure (Shannon & Buckner, 2004). Such findings in isolation have been hitherto challenged to demonstrate a role of the PPC in the multi-featured richness of retrieved episodic memories, as has been supported by this study.

Additionally the use of such coarse measures may merely replicate distinctions in memory performance which are similar to those previously found between neural activity associated with measures of familiarity and recollection (Henson, Rugg, Shallice, Josephs, & Dolan, 1999). These associations thus run the risk of only signifying underlying neural activity which

reflects differences in the potential influence of familiarity or recollection during memory retrieval tasks, rather than providing objective evidence of neural activity which underlies distinctions in the quality of retrieval. The observed findings of increased PPC amplitude with the amount of detail for episodes at retrieval, as well as multi-sensory richness, provides more direct support for the association of the PPC with episodic binding at retrieval.

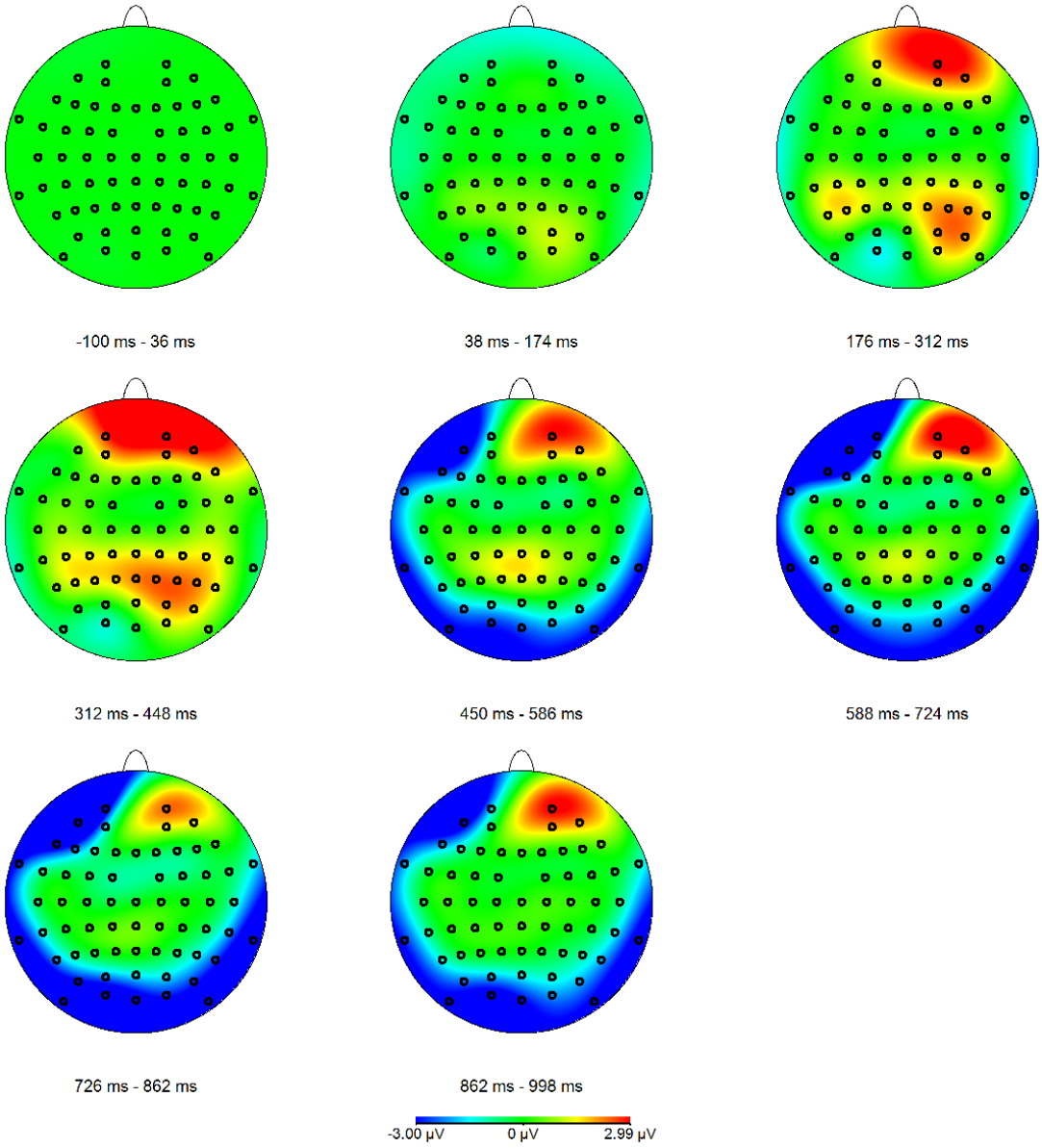

Figure 3. Topography of the Old/New Effect

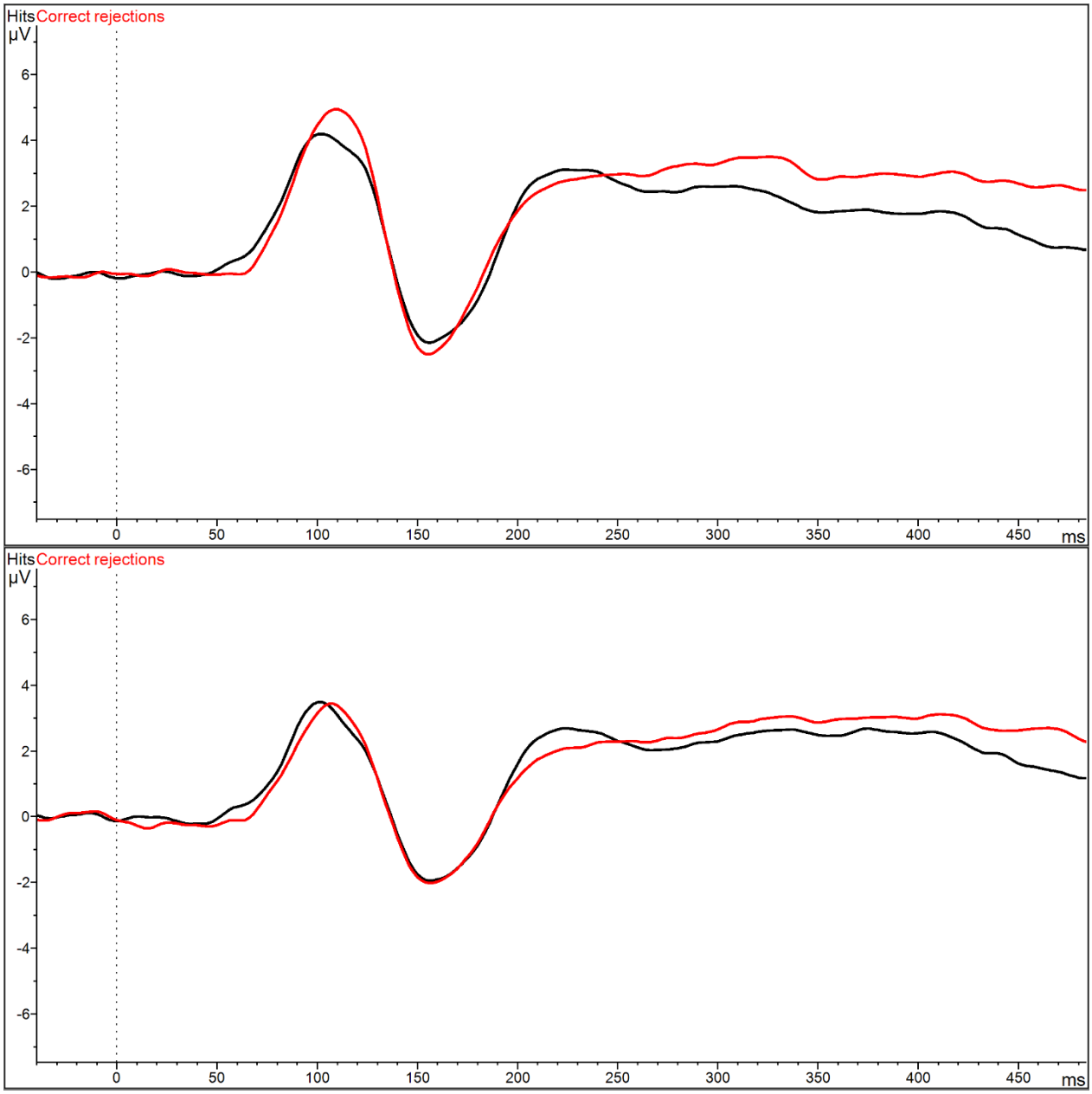

Figure 4. Grand average for Hits and Correct rejections at P3 and P4

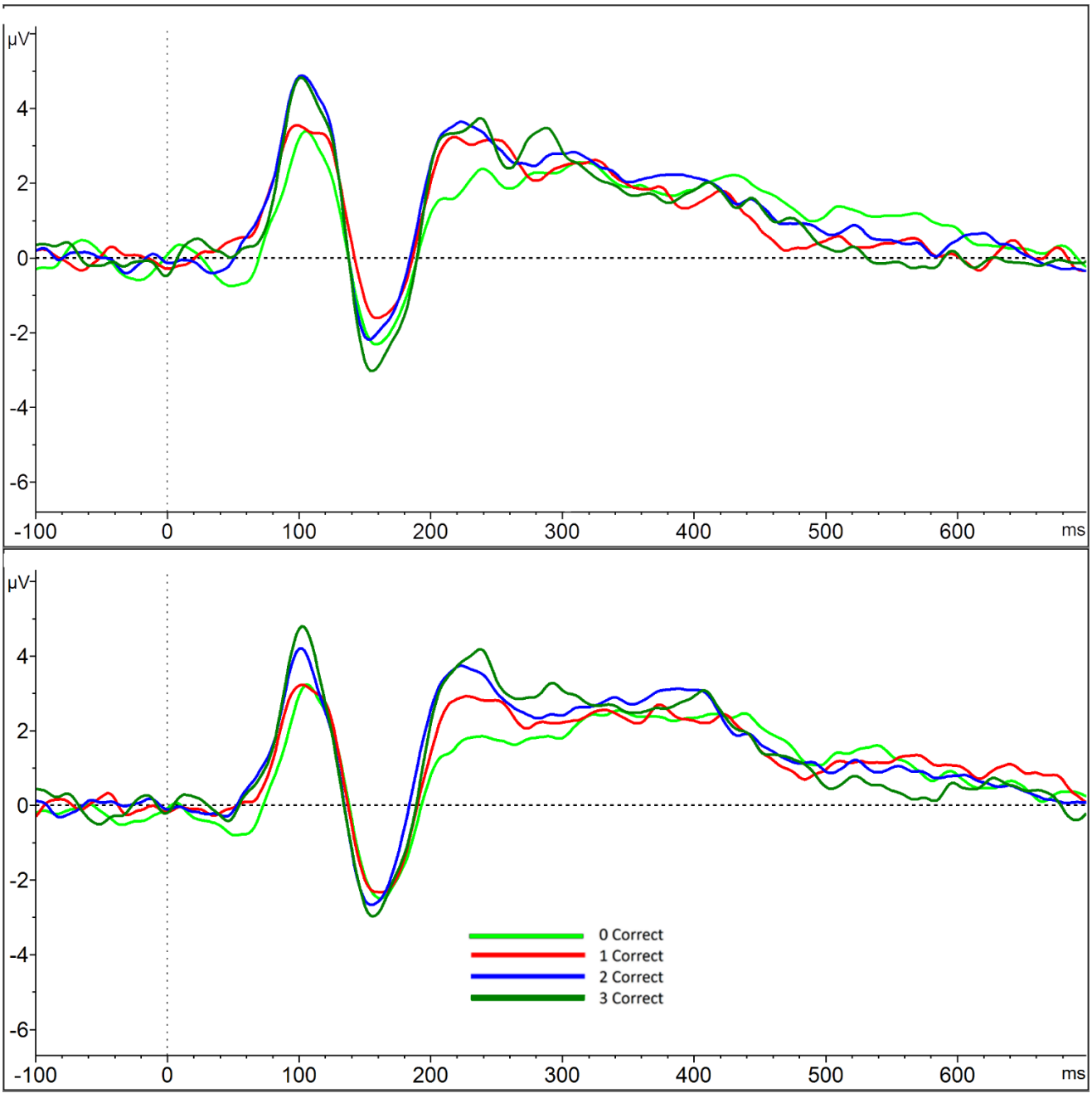

Figure 5. Average ERPs at P3 and P4 for 0, 1, 2, and 3 correct sources

Chapter 4: Dissociation of parietal and frontal correlates of multimodal retrieval

The understanding of processes involved in memory recognition, which is engaged when making a judgment that a stimulus event has been previously experienced, has continually been evaluated in terms of the multiple sources of mnemonic information believed to support this process (Yonelinas, 2002; Rugg & Yonelinas 2003). Interest among experimental psychologists has been heavily concerned with whether one or more than one mnemonic processes are involved. According to single-process accounts recognition judgments are based on the evaluation of a single type of evidence, and a positive judgment is made when the strength of the evidence exceeds a criterion level (Donaldson, 1996). Dual-process like single process theories of recognition memory propose that recognition is supported by the undifferentiated evaluation of a single type of evidence, where positive judgments are made when the strength of the evidence exceeds a criterion level (referred to as familiarity). However, advocates of dual-process accounts argue that recognition relies on a second, functionally distinct, memory signal that results from the retrieval of qualitative information about the study episode (Mandler, 1980). Familiarity-based recognition is generally considered to be fast-acting, relatively automatic and does not provide qualitative information about the study episode. Recollection, by contrast, is conceived as more effortful process that gives rise to consciously accessible information about both the prior occurrence of a given recognised item and the context of that occurrence (Norman & O'Reilly, 2003). Recollection therefore is often discriminated as recognition accompanied by accurate memory for a specific feature of the study context, such as the location or colour of an item, which known as source memory. Another method for segregating recollection from familiarity recognition uses the 'remember/know' procedure, which requires participants to subjectively report whether recognition is accompanied by specific details of the study episode (Tulving, 1985).

In general, it is agreed that the parietal old/new ERP effect is an electrophysiological correlate of recollection-based recognition (Rugg & Curran, 2007), and the topography of this effect is thought to reflect left parietal lobe related activities (Wagner et al., 2005). Source memory studies like the one presented in the previous chapter provide strong evidence about the association between the left parietal effect and recollection. The presence or absence of contextual information is claimed to distinguish between recollection and familiarity (Johnson, Hashtroudi, Lindsay, 1993). That is, contextual information is available in recollection but not familiarity. For such cases, accurate source judgments are used to identify when recollection takes place. Several studies were conducted to investigate whether the old/new effect modulated by source accuracy. For instance, in the study of Wilding and Rugg (1996), participants made old/new judgments followed by subsequent forced-choice source judgments. The results indicated a larger left parietal old/new effect for source-correct trials than source-incorrect trials. A more elaborate manipulation demonstrated that this effect is also sensitive to the amount of retrieved information, and the strength of recollection is graded (Wilding, 2000).

A second Old/New effect, occurring in a similar time range with a frontal scalp distribution, was also observed, however unlike the parietal effect, this 'mid-frontal' effect was also elicited for new items that shared many features with studied items. This effect was further dissociated from the parietal effect in that it was insensitive to source accuracy (Duarte, 2004), and depth-of-study manipulations of recollection (Wilding, 1998). Most critically, it was only elicited for items endorsed as 'known' without recollection of details, and not for items endorsed as being remembered with recollection. These patterns were taken as consistent with the proposal that the parietal Old/New effect is linked to the recollection of specific information, whereas mid-frontal effect is linked to familiarity-driven recognition.

Similar to such findings, the study in the previous chapter also indicated a frontally distributed old/New effect, however this pattern of activity was seen to coincide closely to that observed at posterior sites, as both patterns featured an early onset. Given the equivalent magnitude observed across both effects, and the more sustained frontal distribution (See Figure 3, Chapter 3), it may be possible that the frontal activity also shared

the sensitivity observed over parietal sites, but over a different time window. The current study investigated whether the dissociation of the frontal Old/New effect from the parietal Old/New effect typically observed in ERP studies of recognition memory could be observed within the source memory paradigm reported previously, whereby the graded sensitivity of parietal activity to source retrieval would be distinguished from frontal effects invariant with source. In order to compare the potentially subtle differences in the sensitivity of these Old/New effects to increased retrieval of multimodal contexts, the individual differences in the magnitudes of ERPs for old and new items were measured for each participant. Analyses of the difference ERPs over frontal and posterior electrodes were predicted to reveal a selective sensitivity of parietal effects to the amount of sources retrieved in comparison to that observed for frontal sites.

Method

Participants

Sixteen participants (11 female, aged 19 to 39, mean = 23 years, SD = 4.87) completed a source memory task testing for the audio, visual, and metacognitive contexts of an episode, while undergoing EEG recording. Each was either paid at a rate of £7/hour, or received credit towards fulfilment of an experimental participation requirement for their course. All participants were right-handed, and had no history of neurological or psychiatric disturbances. Participants provided written informed consent in a manner approved by the local department ethics panel. Participants completed the identical source memory task as previously described in the EEG study in Chapter 3, using the same stimuli and procedure.

Procedure

Participants completed five blocks of the source memory task while undergoing EEG recording, with the procedures and materials accounted in the previous methods Chapter 2.

EEG recording and data analysis

EEG was recorded via 2 32-channel DC amplifiers using Brainvision Recorder and ActiCap software (Brain Products, Munich, Germany). For each participant 60 electrodes were

mounted on a cap while two additional ocular electrodes were placed on either side of the face to monitor horizontal eye movements, and two above and below the left eye to monitor vertical eye movements. Electrode impedances were kept under 5 kΩ when possible but were accepted when below 20 kΩ and the sampling acquisition rate was 2000 Hz. The position FCz was the reference electrode during acquisition; TP9 and TP10 were used as references during the analysis. Using Brainvision Analyser Version 2.0. (Brain Products, Munich, Germany), trials contaminated with eye movements and other artefacts beyond correction were rejected. Following a 0.03 to 70Hz band pass filter and 50hz notch filter to remove electrical noise on the raw data, the data were processed through an ICA which identified and corrected for ocular/motion components. For each participant segmentations were made based on markers for the onset of each face presented on a test trial, and baseline corrections were carried out 100ms before stimulus onset before the average was obtained for each condition. In order to examine the differences in anterior and posterior responses to increasing multisensory retrieval of episodes, subtraction ERPs were conducted separately for each participant between the mean ERPs for correct rejection trials and the mean ERPs for the trials with 0,1, 2, and 3 correct source retrievals for recognised items.

Results

Task data

Recognition of faces was high overall, with an accuracy of 0.81(MSE =0.09). Discrimination P (hit) - P (false alarm) was reliably above chance, $t(16) > 9.53$, $p < .001$. Accuracy of source retrievals differed between modalities, $F(2,28) = 18.94$, $p < .001$, with accuracy for face location being the highest at 0.66 (.011) accuracy for task, the second highest at 0.63 (.011) though not significantly different from location ($t(16) = -1.72$, $p = .261$), and accuracy for voice the least at 0.53 (0.48), which differed from accuracy for location ($t(16) = -8.55$, $p < .001$) and task ($t(16) = -6.82$, $p < .001$). Reaction time for correct judgements overall, 1186ms (227), was faster than for incorrect judgements, 1446ms (308), $F(1,28) = 44.82$, $p < .001$. The RTs for recognition decreased when there were 0 source retrievals (950 ms (281)), 1 correct source

retrieval (966ms (33)), 2 correct source retrievals (909ms (26)), (1206ms (270)), and 3 source retrievals (900ms (36)), however these weren't reliable differences, $F(3,16) = 0.849$, $p > .4$.

ERP Data

ERPs were formed for correct retrievals and rejections trials as detailed earlier in the methods chapter, and were used to form subtraction ERPs for each participant of correct rejections from correct source retrieval categories. The grand average subtraction ERP for all of the successful recognition and correct rejections trials manifested a sustained positivity arising ~150-400 ms, with maximal amplitudes over the right anterior and left posterior sites (Figure 6.). In order to identify differences between the anterior and posterior sensitivity of the Old/New recognition to increasing recollection of multisensory contexts, analyses was performed on the ERPs from a selection of electrodes from frontal and parietal lobes in both hemispheres. Frontal electrodes comprised AF4, F1, F2, F3, F4, F5, F6, F7, F8, FC3, FC4, and Fz, and parietal electrodes comprised CP1, CP2, CPz, P1, P2, P3, P4, P5, P6, P7, P8, and Pz. Participants were excluded if they had insufficient (10 or less) artefact-free trials to contribute to ERPs in any of the categories, for a total of 16. The peak potentials were calculated for each participant's subtraction ERP of correct rejections and source retrievals over a 200-600ms post-stimulus epoch at each electrode site. A global ANOVA was conducted including the factors of source accuracy, hemisphere, and frontal/parietal lobes. The interactions of lobe, site, and hemisphere with source accuracy were analysed in follow up separate ANOVAs within each lobe. Greenhouse–Geisser corrected degrees of freedom were used for all ANOVAs. There were significant main effects of source accuracy and lobe, but not hemisphere, reflecting greater change in ERPs with increased source retrievals ($F(2.26,13)= 132.554$, $p<0.001$), and an overall greater change in parietal lobe difference ERPs compared to those of the frontal lobe ($F(1,14)= 63.895$, $p<0.001$). An interaction of source accuracy with hemisphere was found to be two-fold ($F(2.26,11)= 7.714$, $p<0.001$). Separate ANOVAs of parietal and frontal lobes, and the two hemispheres revealed that the overall mean change in ERPs with source retrieval was greatest for the parietal lobe in the left hemisphere ($F(1,14)= 36.957$, $p<0.001$) thought not significantly different from the right

hemisphere ($F(1,14)= 0.348277$, $p>0.5$), and in conversely the mean change in ERPs was least for the frontal lobe in the left hemisphere, however this significantly differed from those of the right hemisphere ($F(1,14)= 3.944$, $p<0.001$). Grand Average difference ERP waveforms from representative frontal and parietal sites are shown in Figure 7. There was a significant interaction of lobe with the effect of source accuracy ($F(2.26,11)= 7.714$, $p<0.001$), and subsidiary separate ANOVAs of frontal and parietal lobes revealed significant but different main effects of source accuracy for the difference ERPs, ($F(2.175,14)= 15.884$, $p<0.001$, and $F(1.613,14)= 24.689$, $p<0.001$, respectively) as seen in Figure 8. Over the frontal lobe the change in difference ERPs increased significantly from trials with 0 correct sources to those with 1 correct source ($t(14)= -3.343$, $p=0.02$), but decreased significantly from trials with 1 correct source retrieval to those with 2 correct sources ($t(14)= 3.279$, $p=0.02$). Furthermore the change in ERPs did not significantly differ from trials with 0 to 2 correct sources ($t(14)= -1.520$, $p>0.5$), however they significantly increased from trials with 2 correct sources to 3 correct sources ($t(14)= -5.052$, $p<0.001$). In contrast, the change in difference ERPs in the parietal lobe with retrieval of correct source was consistently positive. These changes increased from 0 correct to 1 correct source trials ($t(14)= -4.960$, $p<0.001$), did not significantly differ from 1 correct source to 2 correct source trials ($t(14)= 0.831$, $p>0.5$), and showed further increase from 2 correct source to 3 correct source retrievals ($t(14)= -9.155$, $p<0.001$). This effect of source accuracy did not differ between hemispheres of the parietal lobe, however this effect was attenuated in the left hemisphere of the frontal lobe ($F(1,14)= 3.944$, $p<0.05$) though the trend was the same.

Discussion

The ERP results affirm the findings of the previous chapter that posterior parietal EEG responses are directly associated with increased contextual richness of retrieved episodes. The Old/New effects of accurate source retrieval previously observed in the PPC were found to be driven by changes in the magnitude of ERPs for retrieval of episodes with increasing detail. These ERP changes differed from those underlying frontal Old/New effects observed in a similar time window not only in terms of greater magnitude, but also in sensitivity to increased source retrieval. Frontal sites showed a change in the responses to accurate

retrieval that sometimes decreased in ERP magnitude with increased amount of source detail whereas parietal sites showed unidirectional increases with the number of sources participants retrieved on trials. This distinction supports previous findings that retrieval activity over the PPC reflects recollection of rich memory episodes, and frontal retrieval activity distinguishes recognition accuracy, but recollection quality to a lesser extent (Curran et al., 2007). The latencies of the peak differences between ERPs for correct rejections and hits were seen to overlap in time with the typical P200 ERP component, which has been observed in memory retrieval paradigms. However within the ERP categories no waveforms were seen to follow that would distinguish these early positive ERPs from a separate Old/New posterior effect. The P200 component has typically been implicated in early availability of lexical access during word processing (Dambacher et al., 2006), and demonstrates sensitivity to the strength of the semantic relation between recognised words and their immediate context (Stuellein, Radach, Jacobs, & Hofmann, 2016), but also is mediated by familiarity characteristics such as word frequency (Hauk & Pulvermueller, 2004). There have however been some reports that this component can distinguish similar qualities of memory retrieval, though only to a coarse extent (Tanguay, et al., 2018). This sensitivity was further limited to central, and not posterior, parietal sites and it largely served to mediate the similar sensitivity of a later posterior component observed in a latency range typical of the Old/New parietal effect. However, as previously demonstrated in Figure 5, the ERP categories investigated in our paradigm display a posterior positivity sustained for 200ms, typical of the Old/New effect, but earlier in onset, which has occurred in other recognition memory tasks (Vilberg, Moosavi and Rugg, 2006; Duarte et al., 2004; Tsivilis et al., 2001). No later positivity following this effect was observed, and this sole sustained positivity distinguished between the fine differences of the source memory categories. The results of the subtraction ERPs (Figure 7) indicate that a difference in earlier latencies further distinguished the sensitivity of the left posterior parietal response to multimodal episodic retrieval.

According to single-process accounts recognition judgments are based on the evaluation of a single type of evidence, and a positive judgment is made when the strength of the

evidence exceeds a criterion level (Donaldson, 1996). Dual-process like single process theories of recognition memory propose that recognition is supported by the undifferentiated evaluation of a single type of evidence, where positive judgments are made when the strength of the evidence exceeds a criterion level (referred to as familiarity). However, advocates of dual-process accounts argue that recognition also relies on a second, functionally distinct, memory signal that results from the retrieval of qualitative information about the study episode. Within this model the retrieval of such episodic information in response to a recognition test item is referred to as recollection (Yonelinas, 2002). The functional distinctiveness of this process from familiarity has been challenged by Parks and Yonelinas (2007) that recollection is best conceptualized as also representing a discrete mnemonic state that is thresholded in an all or none manner, whereas others have suggested that familiarity and recollection are both continuously varying memory signals that can be collectively recruited for a recognition judgement (Wixted, 2007). Findings from several early studies suggested that recollection has an ERP signature, often termed the 'parietal' old/new effect. This effect is distinguished from a midfrontal old/new effect in that it can be modulated according to whether the recognised items are associated with successful or unsuccessful source judgments (Wilding & Rugg 1996; Senkfor & Van Petten, 1998; Woodruff et al., 2006), whereas frontal effects associated more with familiarity distinctions or more coarse recognition, similar to the distinction in the old/new effects observed here. For example, the parietal old/new effect was found to be greater when elicited by test items accompanied by successful versus unsuccessful source memory. Findings from further studies suggest that the left parietal old/new effect is likewise sensitive to the varying amount of information recollected, and is not an all or none response (e.g., Rugg et al., 1995, 1996; Wilding, 2000).

However there remains uncertainty in the interpretation of such reports of continuous graded parietal old/new effects. It is not possible to rule out for these studies that the difference in the magnitude of the parietal old/new effect in the averaged ERPs merely reflected a corresponding difference in the proportion of trials contributing an all-or-none recollection response. Such a case is the recent study in which the parietal old/new effect was found to

be greater for response conditions in which participants made 2 compared to 1 successful source retrievals for recognised words (Wilding, 2000). If all recollected items were accompanied by equivalent all or none parietal ERPs, then the mean ERPs for these response conditions would only vary by the number correctly guessed responses that did not exhibit an old/new effect. Since participants in this study rarely recognised an item without identifying at least one correct source (less than %15 of responses), it is possible to view the response condition with 1 successful source as reflecting a combination of responses with recollection for which participants could retrieve all sources, but made source errors for erroneous reasons, and responses for which participants did not recollect the item, but accurately guessed the item and a source. In contrast their response condition with 2 successful source retrievals would reflect recollection responses as well as a proportion of non-recollected but correctly guessed items and sources, for which the probability of guessing through chance alone would be half that of the former response condition (20 and 12.5% respectively). It therefore remains a possibility that the observed difference in ERPs arose from an increased proportion of responses for correct guesses in the response condition with 1 successful source retrieval which did not elicit an old/new effect, and consequently reduced the ERP mean for this condition compared to those for 2 successful source retrievals.

The current study however precludes this possibility as a potential explanation of the effect of increased source. Since the probability of correctly guessing 2 or all 3 sources by chance alone is quite low, the proportion of guessed responses contributing to the 2 source retrievals ERPs would not differ significantly from that of the 3 source retrievals ERPs. Therefore, if the ERPs for successful recognition had an all-or-none response compared to guessed trials, but didn't vary with the amount of source retrieved, then the significant increase for 3 source retrievals ERPs from those for 2 source retrievals would not have been observed by chance alone, whereas the increase in 2 source retrievals ERPs from 1 source retrieval ERPs might have been observed. The evidence provided by these findings of an Old/New response reflecting graded recollection thus proves more resilient to alternative

accounts than the previous studies with similar indications of continuous Old/New recollection response (Wilding 2000).

The findings from the current study demonstrate a graded sensitivity of the response over parietal sites with uniquely direct measures of objective differences in the amount of information retrieved from episodes. Previous findings associating the parietal Old/New effect with the continuous quality of episodic retrieval frequently conversely relied on distinctions based on subjective, or indirect association of retrieval quality. Vilberg, Moosavi, and Rugg (2006) likewise demonstrated a graded modulation of ERPs by the amount of contextual information retrieved by having participants subjectively discriminate between pictures they remembered with some detail, pictures they remembered with detail and their paired associate, and familiar pictures they knew although they couldn't recall any details. They found that the magnitude of the Old/New effect over left parietal sites increased with the detail of the information participants claimed to retrieve about old pictures, which was distinguished from an earlier onsetting left frontal Old/New effect which did not differ with detail claimed. These findings make distinctions in electrophysiological profiles associated with the subjective experiences that participants had for differing degrees of episodic retrieval, however they do not provide direct evidence of differences in actual amount of information retrieved.

In a subsequent attempt to relate the findings to objective differences in the information retrieved, a further investigation examined the modulation of the parietal ERPs under conditions which made retrieval of information more or less likely (Vilberg & Rugg, 2009). Participants in this study discriminated between pictures of objects they could remember with details, and those that they knew they had seen, but could not recall further details at test. The study manipulated retrieval success by decreasing the length of time participants had to encode items, whereby participants overall recalled less information about objects studied for 1 s compared to objects studied for 6s. The findings indicated that the left parietal old/new effect had a greater magnitude for old objects studied for 6 s which participants claimed they remembered compared to those studied for 1 s. Although post-study testing provided strong support that overall participants retrieved more episodic details for

remembered objects studied for 6 s, these measures could not directly account for the amount of episodic details retrieved during the test trials that were included in the ERPs. Only an indirect association of the observed ERP differences can therefore be made with the object amount of episodic details participants retrieved, and it does not exclude other factors that may have led to larger Old/New effects for the objects studied for 6 s.

Most recently a multimodal imaging study similarly examined the modulation of the parietal ERPs with multisensory source retrieval (Bergstrom et al., 2013). Much like the current investigation, participants encoded faces under two different task contexts, either a pleasantness judgement or a judgement of the British nationality of the presented face. They further encoded the face location on the left or right of the screen by judging the proximity of the face to centre of the screen. At test participants identified either the task context, or location context of studied faces, or they made a semantic judgement about the occupational status of the presented face as an entertainer. Unlike the previous studies, the authors did not directly examine the magnitude of the Old/New effect for ERPs during retrieval, but instead compared the ERPs for retrieval of the two sources with those for the semantic judgement. They found that late parietal ERPs significantly increased with objective retrieval of one source compared to retrieval of semantic information. They further found that the magnitude of ERPs for retrieval of task contexts was greater than that for retrieval of location contexts. These findings indicate a graded response of parietal ERPs for objectively distinct classes of retrieval, however on their own they cannot account for objective differences in the quality or episodic detail of retrieval. Similar to the previously discussed studies, the effects observed were not due to differences in the objective amount of episodic details at retrieval, but instead were based on differences between semantic retrieval and retrieval of source, which reflect distinct memory processes.

Despite their use of subjective or indirect differentiations of the quality of episodic retrieval, the distinction these studies made in the topography and latency of electrophysiological response during retrieval strongly resembles those of the current study. The late posterior parietal ERP Old/New effect was found to closely reflect the amount and richness of episodic details retrieved, as previous studies (Wilding & Rugg 1996; Senkfor & Van Petten, 1998;

Curran, 2004; Duzel et al., 1997) found for responses associated with recollection of increasing strength. This was however distinguished from the pattern of a frontal Old/New effect, which only coarsely discriminated between certain amounts of retrieved episodic details, as had been observed for discriminations between old and new items, but not between familiar and recollected items (Woodruff et al., 2006; Groh-Bordin et al., 2006; Nessler et al., 2005; Curran & Dien, 2003). The current study therefore supports the inference made by previous researchers (Vilberg & Rugg, 2009; Bergstrom et al., 2013; Vilberg, Moosavi, & Rugg, 2006) that the modulation of the Old/New ERP component by differences in subjective or indirect measures of retrieval quality reflect a sensitivity to the objective amounts of episodic detail participants retrieved.

Further to specifying this graded sensitivity of episodic richness to PPC activity, the analysis of the subtraction ERPs also indicates that the modulation of this activity by objective retrieval was somewhat greater for the left hemisphere of this region. In contrast, modulation of the Old/New effect over frontal sites was found to be significantly greater for the right hemisphere, though only for coarse discriminations in amounts of retrieval. This elucidates a topographic distinction between the magnitude of response for increased retrieval of episodic details demonstrated in the previous chapter, and the magnitude of change in response with episodic detail currently observed. Here the trend towards a hemispheric asymmetry over the PPC was found for the left hemisphere, and not the right as was found in the former chapter, suggesting that the Old/New ERP over the left may be smaller, but more closely tracks successful retrieval of multimodal contexts than the right PPC. This corroborates the finding from studies of that the Old/New effect exhibits a left hemisphere maximum over the PPC to recollective responses. The activity from this region is therefore implicated in a continuous integration of multimodal details during episodic retrieval, as predicted by theories that the PPC serves as a convergence zone of active cortical representations (Shimamura, 2011), and supported by the findings of the previous chapter.

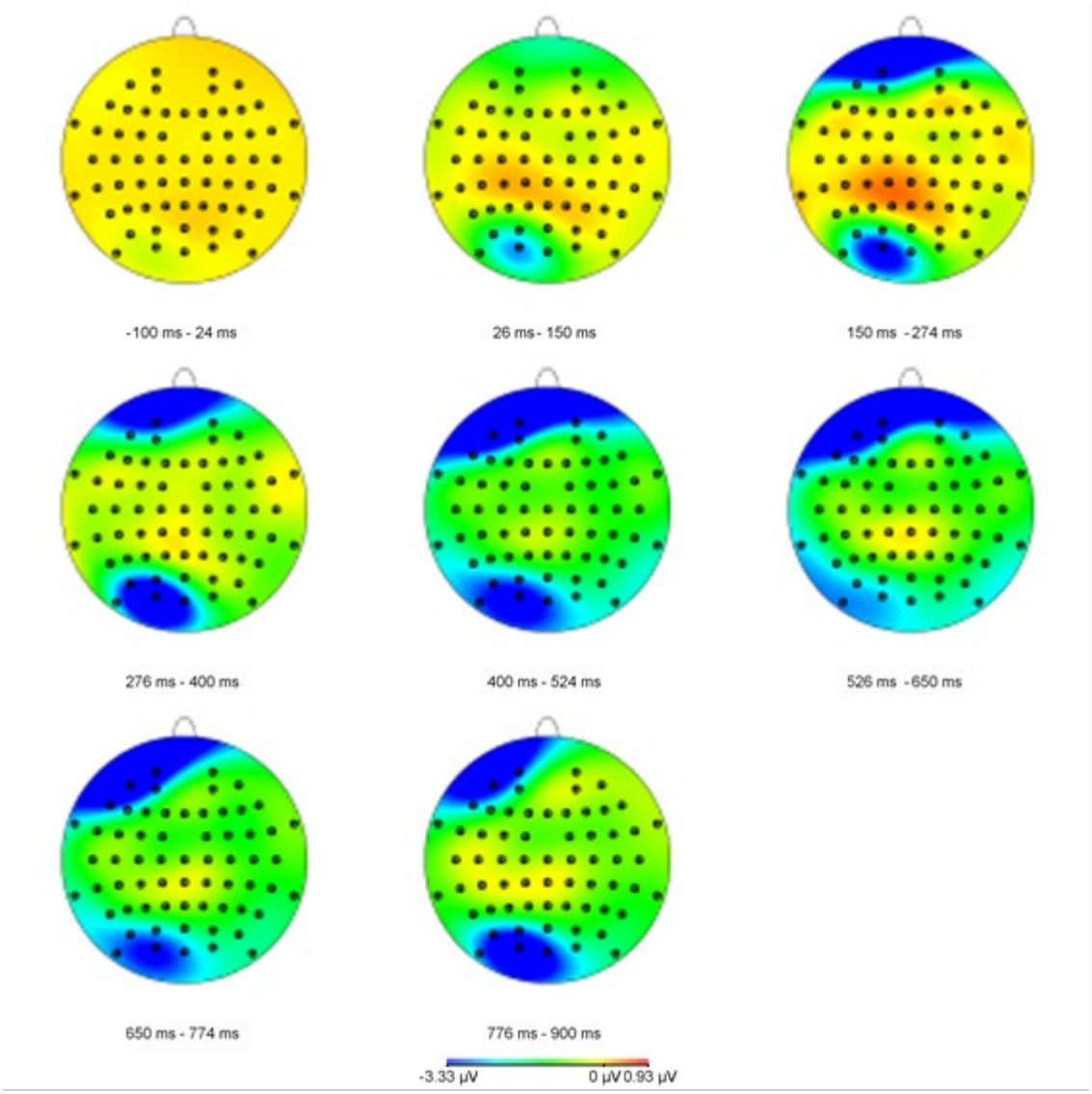

Figure 6. Mean topographic distribution for the subtraction of correct rejection ERPs from Hit ERPs

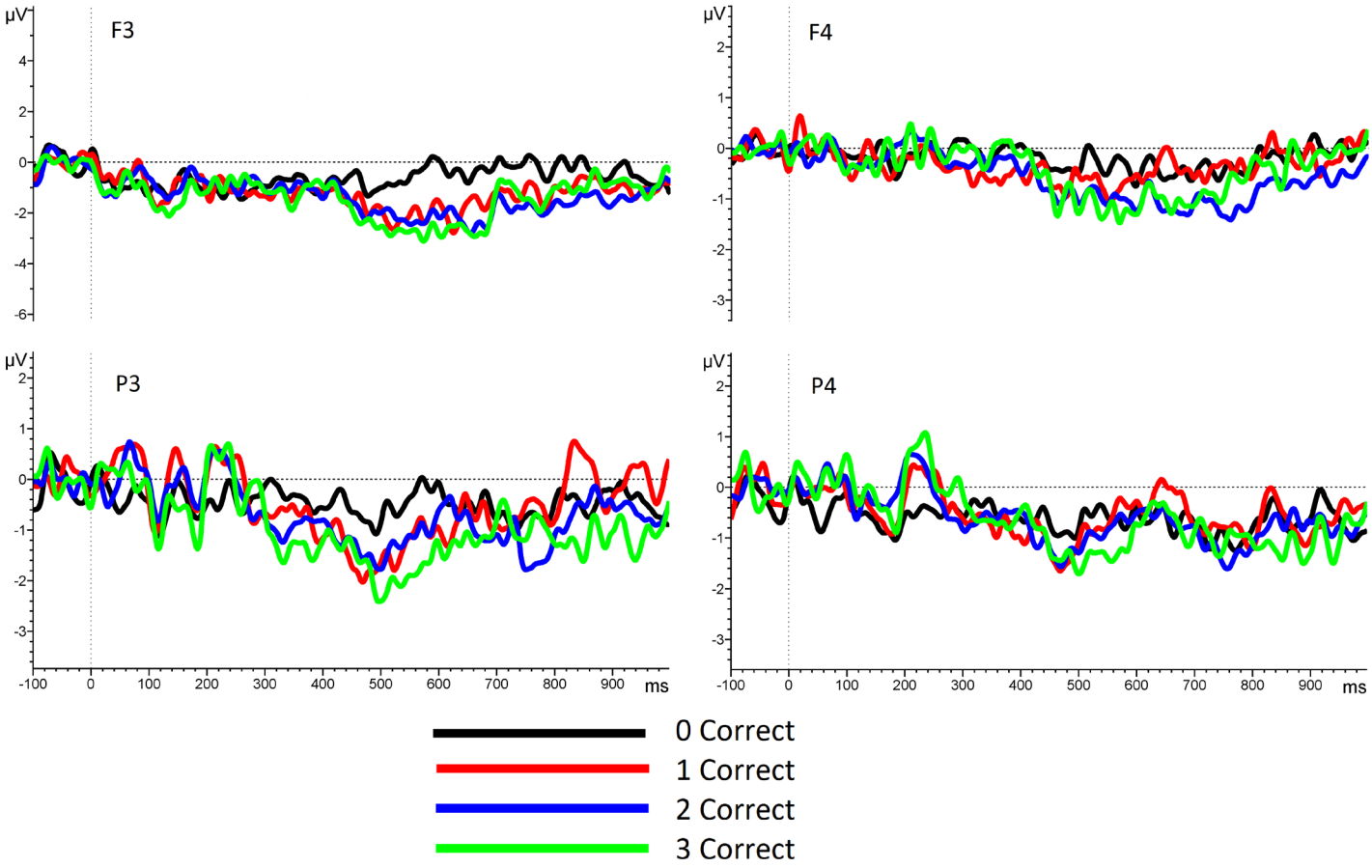

Figure 7. Grand Average difference ERPs between correct rejections and hits with 0, 1, 2, and 3 correct source retrievals. Waveforms from representative frontal and parietal electrodes.

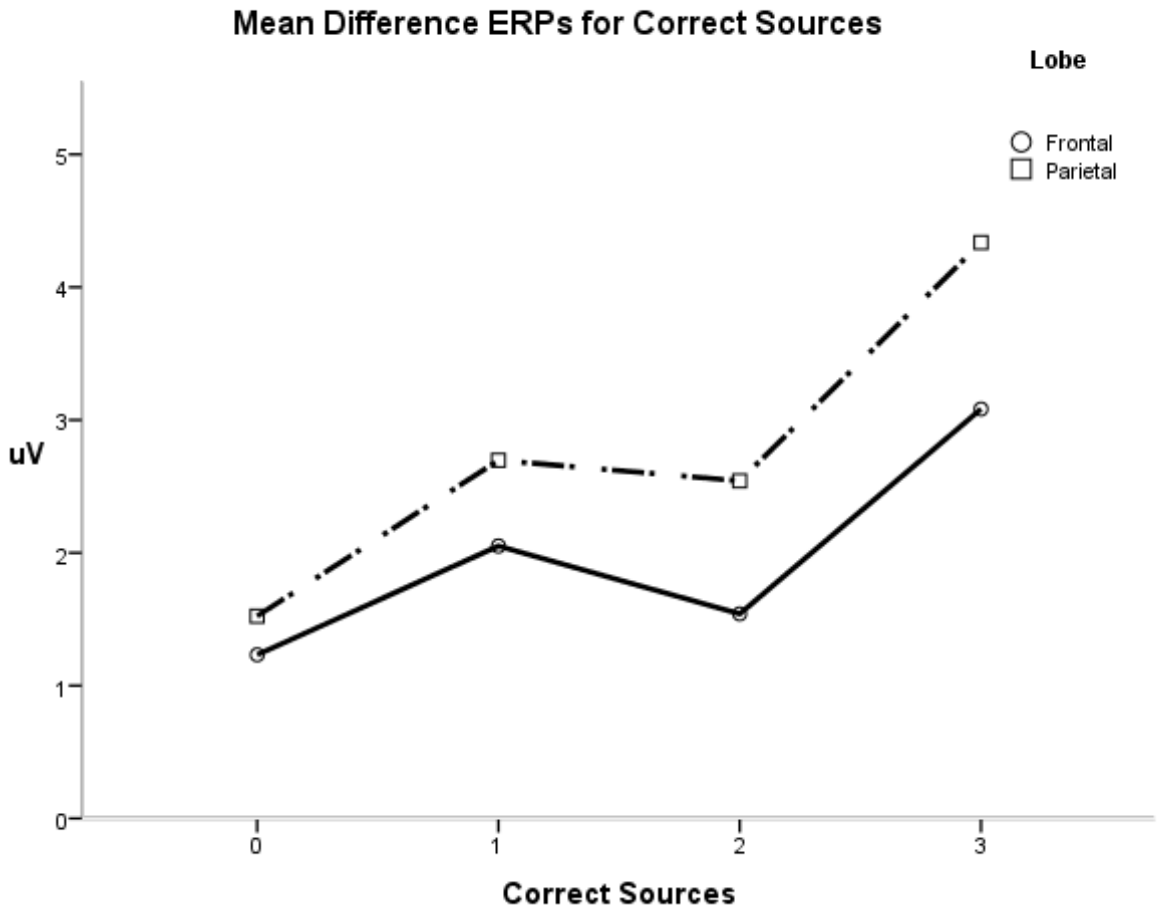

Figure 8. Mean peak amplitude of the difference ERPs for correct rejections and hits with increasing number of correctly retrieved sources averaged for frontal and parietal electrodes separately

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Chapter 5: Effect of posterior parietal stimulation on episodic retrieval: a tDCS investigation

Previous work indicating an association of PPC activity with behavioural measures of episodic retrieval have predominantly only demonstrated relations with indirect measures of neural recruitment (Ranganath & Ritchey, 2012), including the ERP study we conducted. Similarly, the findings of our study are the first to demonstrate a clear association of the PPC with binding of multimodal contexts within an episode, yet this was accomplished through the of use electrophysiological measures indirectly associated with PPC function. Such associations, however robust, may be taken to indicate only an involvement of the PPC, and not the PPC's specific role, in binding retrieved contexts (Shimamura, 2011).

The literature in cognitive neuroscience on the contribution of brain regions or networks in higher cognitive functions has predominantly demonstrated relations between indirect measures of neural recruitment (e.g. changes in scalp electrical potential) and cognitive function. Recently however, directed neuronal plasticity has become a central topic in cognitive neuroscience. Plastic changes (i.e. the strengthening of neuronal connections and the re−organisation of neural networks) can be evoked by practice, rehabilitation or even with external stimulation, and they are found to underlie changes in cognitive function. In humans, the use of non-invasive external neurostimulation techniques to induce plastic changes has allowed for predictions of cognitive neuroscience to be directly explored (Dayan et al., 2013, Sandrini et al., 2011).

In the last few decades, tDCS has been considered as a tool for modulating cortical excitability and behaviour (Stagg & Nitsche, 2011). It is a non-invasive electrical brain stimulation method, in which direct currents pass through scalp electrodes and induce a temporarily cortical excitability shifting. Depending on current polarity, the resting membrane potentials are modified by a tonic depolarization or hyperpolarization (Nitsche et al., 2008). In general, cerebral excitability was increased by anodal stimulation, which depolarizes membrane potentials. In contrast, cathodal stimulation caused membrane hyperpolarization, resulting to a decreasing cerebral excitability (Bindman et al., 1962; Nitsche & Paulus, 2001).

Given the advantages of tDCS, this technique has been wildly applied on neuropsychological treatment (Hummel et al., 2005; Frengi et al., 2006; Boggio et al., 2008) and experimental conditions (Nitche et al., 2008; Hsu et al., 2011). This presents convenient and easily-operated technique for modulating cortical excitability.

The previous studies found a find-grained sensitivity of the increased neurophysiological activity over the PPC to the richness of episodic retrieval during our multimodal source memory task. In our subsequent study we directly investigated the causal nature of such PPC activation in episodic retrieval by employing tDCS in the same multimodal source memory paradigm. As anodal and cathodal tDCS stimulation are known to increase and decrease neuronal excitability over a broad region respectively, it was predicted that if the PPC is necessary for multimodal binding of episodic contexts, such stimulation over this region with anodal or cathodal electrodes should lead to a concomitant increase or decrease in successful source memory performance during the task.

Methods

Participants

Thirty participants (16 female, aged 19 to 39, mean = 23 years) completed the previously used source memory task testing for multimodal retrieval. Each was either paid at a rate of £7/hour, or received credit towards fulfilment of an experimental participation requirement for their course. All participants were right-handed, had no history of neurological or psychiatric disturbances, and did not meet any criteria of contraindications for safe use of tDCS (Nitsche, 2008). These criteria include history of drug abuse, fainting, or migraines, pregnancy, being a licensed HGV driver, or having any metallic implant in the neck, head or eye, or any other implanted electrical device. Participants provided written informed consent in a manner approved by the local department ethics. They were divided into two groups, with 15 participants in the anodal group, which received active anodal tDCS and sham stimulation, and 15 participants in the cathodal group, which received active cathodal tDCS and sham stimulation.

Stimuli

Two hundred and fifty-six black and white photographs of faces (64 of famous celebrities, 192 from the Glasgow Unfamiliar Face Database (2010)) were used for the visual stimuli. The 64 famous and 64 nonfamous faces shown during study phases were matched in proportion on age, gender, and ethnicity, as were the 128 nonfamous faces only shown during test phases. Presentation order of faces was randomised between participants. Four audio recordings were used for auditory stimuli, one of each task question spoken by a male, and one of each task question spoken by a female.

Procedure

Participants completed four blocks of the source memory task previously used in our ERP study and received active tDCS and sham tDCS on two blocks each, according to their current polarity group (anodal, cathodal). The source memory task consisted of two phases, a study and a test phase, and participants completed five blocks of study-test cycles while undergoing EEG recording. On study phase trials participants were presented with a fixation cross at the centre of the screen for 1000ms. Then a famous personality or an unfamiliar face was presented either to left or right side parallel to the fixation cross for 1sec, at which point participants were presented with the face of either a famous personality or an unfamiliar person, and were asked 2000ms question to perform one of two tasks via headphones. In the pleasantness task participants were asked to indicate if the face was pleasant or not. In the celebrity task they were asked to indicate if the face was of a celebrity or not. This was followed by a second screen with instructions to indicate on which side the face was shown, and a third to indicate the gender of the questioner, both preceded by presentation of a fixation cross for 100ms. They received on-screen instructions to indicate a choice by pressing the “c”, or the “m” key on the keyboard as quickly as possible up to a maximum of 2400ms. Each study phase lasted 32 trials and after they had been completed participants then received instructions to begin the test phase. Stimulation was administered during the study phase according to current polarity group (anodal, or cathodal).

In the test phase participants saw all faces from the study phase, as well as 32 new faces previously shown and were tested on their source memory for studied faces. On test trials

participants first were presented with a fixation cross at the centre of the screen for 1000ms, followed by a face for another 1000ms, to which they were instructed on screen to indicate whether it had been previously presented at study for a maximum of 2400ms. This was then followed by a second on-screen instruction to indicate which rating task they had completed for the given face, a third to indicate on which side the face was shown, and a fourth to indicated the gender of the questioner, each for a maximum of 2400ms, and preceded by presentation of a fixation cross for 100ms. For trials for which a new face stimulus was presented participants could press any key to respond for the last three indications. The test phase lasted 64 trials, and concluded the block, after which participants had the option to take a break before beginning the next block.

Transcranial direct current stimulation protocol

A CE-certified tDCS medical device was applied in this experiment with a small battery-driven constant current stimulator (BrainSTIM Transcranial Stimulator, EMS medical, UK). The stimulator consisted of a stimulator machine and a pair of conductive rubber electrodes (5cm X 5cm) inside two saline-soaked sponges that were secured on to the skin. One electrode was placed on the P3 site of the International 10-20 System for EEG electrode placement (Jasper, 1958) to stimulate the left posterior parietal cortex, and the other on the right cheek to serve as the reference (Jones & Berryhill, 2012; Tseng et al., 2012). In the active stimulation (on the P3 site) blocks, a constant current of 1.5 mA began at the onset of the study phase for each block and persisted for 4 minutes after the last study trial, lasting for a total of 10 min for each block. In the sham condition, the electrodes were also kept in place for the 10-minute interval but the current was applied only for the first 30 seconds. The fade-in and fade-out durations were 15 seconds for active and sham stimulation conditions. The stimulation alternated between active and sham stimulation type between blocks (two blocks each), with constant electrode placement throughout the experiment, according to the current polarity participant group.

Safety of tDCS depends on both current density and stimulation strength (Nitsche et al., 2003). The current density induced by the tDCS protocol in the present study was a

maximum of 0.0428 mA/cm2, which was well below the safety value of 25 mA/cm2 (McCreery et al., 1990). In regard to the stimulation strength, the total charge was 0.0056 C/cm2. This value was also far below 216 C/cm2, which has been found to have no significant heating effect at the electrode site (Nitsche & Paulus, 2000), or evidence of any neuronal damage (Nitsche & Paulus, 2001; Nitsche et al., 2003). The tDCS protocol used in the current experiment was therefore in accordance with the literature and safe for the participants. Debriefing and questionnaires following the study verified that participants had not experienced any discomfort or irritation from tDCS. The experiments were approved by the local ethical committee.

Control Experiment: tDCS Effects over the Primary Motor Cortex

A subsequent experiment was conducted to ensure the specificity of the main experiment's effect to modulations over the PPC scalp, and not tertiary effects of tDCS such as the physical sensations, or the flow of current across the scalp. An adjacent control site was selected (M1) for stimulation instead of the PPC. Previous research has already demonstrated that it can be readily modulated by tDCS (Reis et al., 2009; Nitsche and Paus, 2001), and given its left-sided location closely along the path of the PPC montage from the main experiment, it consequently serves as an ideal control site. Another group of participants was recruited to complete an experimental protocol identical to the main experiment, except that the tDCS montage was applied over the left primary motor cortex (M1).

Participants

Twenty participants (9 female, aged 19 to 36, mean = 22 years) were recruited with the same criteria in the main experiment. They were divided into two groups with 10 participants in the anodal group, receiving active anodal tDCS and sham stimulation, and 10 participants in the cathodal group which received active cathodal tDCS and sham stimulation.

Procedures

The stimuli and the procedure were identical to those employed in the main experiment. The apparatus and parameters of the tDCS previous ERP study stimulation were employed as in the main experiment. However the active electrode was placed across the scalp above the left m1 cortical site, which was marked 5 cm left relative to Cz (Wassermann et al., 1996).

Results

Main Experiment

Recognition memory

Accuracy of participants for recognition test trials was investigated for old and new faces. A between subjects ANOVA was performed with the factors of polarity group (Anodal, Cathodal), stimulation condition (sham, active tDCS), and item type (old, new). The main effect of stimulation was not significant $F(1,28)= 1.42$, $p=0.23$), nor was the main effect of polarity group ($F(1,28) = 1.39$, $p = 0.24$). There was a main effect of item type, reflecting that overall accuracy of (old) hits (0.804, SE=0.007) was much higher than for (new) correct rejections (0.760, SE = 0.007), $F(1,28) = 20.66$, $p < 0.001$. There was a significant three-way interaction between polarity group, stimulation, and item type, $F(1,28) = 7.90$, $p < 0.001$, and within subject analyses revealed that the after anodal active stimulation participants showed a significant lower rate of correct rejections $F(1,28) = 7.44$, $p<0.01$. There were however no significant interaction effects involving the old items, revealing no evidence that tDCS to the PPC modulated retrieval of old items.

Reaction time

The mean reaction times on test trials was investigated for responses to old and new faces (Figure 9). A between subject ANOVA was performed with the factors of polarity group (Anodal, Cathodal), stimulation condition (sham, active tDCS), and item type (old, new). The main effect of stimulation was not significant $F(1,28)= 1.17$, $p = 0.28$, however the main effect of polarity revealed that the Anodal group (1092.35ms, MSE = 14.15) had significantly slower reaction times than the Cathodal group (945.38ms, MSE =13.33), ($F(1,28) = 56.3$, $p< 0.001$. There was also a main effect of item type, reflecting that overall reaction time for old

items (1050.61ms, MSE = 13.75) was much slower than for new items (987.85ms, MSE =13.75), F(1,28) = 10.416, p = 0.001. A significant three-way interaction between polarity group, stimulation, and item type, F(1,28) = 7.90, p < 0.001 revealed that after anodal active stimulation participants were significantly faster (1039.81ms, MSE = 26.26) responding to old faces than after sham stimulation (1110.91ms, MSE =26.21), F(1,28) = 3.61, p=0.05. Conversely after anodal stimulation responses to new items were significantly faster 3

(1039.81ms, MSE = 26.26) compared to sham stimulation (1110.91ms, MSE = 25.77), F(1,28) = 67.32, p<0.001.

Source memory accuracy

The source memory performance of participants was assessed with the mean accuracy on the memory judgements for old items correctly recognised with one or more source contexts for each trial (Figure 10). A between subject ANOVA of mean source accuracy for trials employing polarity group (Anodal, Cathodal), and stimulation (sham, active tDCS) yielded no significant main effects of current polarity group F(1,28)= 1.648, p=0.20, or stimulation condition *F(*1,46) = 0.61, or related interaction, *F(*1,46) = 2.846, *p* =0.09 . Within-group analyses employing the factor of stimulation were conducted separately for the Anodal and Cathodal groups. In the Anodal group, the effect of stimulation was significant. Analyses of effects of stimulation within groups showed that effect of active cathodal tDCS on mean source accuracy (0.57, MSE= 0.015) did not differ significantly from sham stimulation (0.57, MSE = 0.015), F(1,28) =0.086, p = 0.77. The effect of stimulation on performance of the Anodal group (0.58, MSE = 0.016) however was significant, reflecting a higher mean source accuracy than the sham condition (0.54, MSE= 0.015), F(1, 18) = 4.18, p= 0.04.

Control Experiment Results

Recognition memory

Accuracy of participants on recognition test trials was investigated for old and new faces. A between subjects ANOVA was performed with the factors of polarity group (Anodal, Cathodal), stimulation condition (sham, active tDCS), and item type (old, new). The main

effect of stimulation was not significant, F(1,18)= 0 .44, p = 0.51, however there was a difference between the Anodal (0.71, MSE=0.01), and the Cathodal group (0.81, MSE =0.01), F(1,18) = 70.872, p<0.001. There was a main effect of item type, reflecting that overall accuracy of (old) hits (0.79, MSE=0.01) was much higher than for (new) correct rejections (0.74, MSE = 0.01), F(1,18) = 16.345, p < 0.001. There was a significant three-way interaction between polarity group, stimulation, and item type, F(1,28) = 7.90, p < 0.001, and within subject analyses revealed that after anodal active stimulation participants showed a significantly higher rate of accurate hits F(1,18) = 9.93, p< 0.01.

Reaction time

The mean reaction time on test trials was investigated for responses to old and new faces (Figure 11). A between subject ANOVA was performed with the factors of polarity group (Anodal, Cathodal), stimulation condition (sham, active tDCS), and item type (old, new). The main effect of stimulation was not significant F(1,18)=0 .584, p =0.45, however the main effect of polarity revealed that the Anodal group (922.101ms, MSE = 13.23) had significantly slower reaction times than the Cathodal group (810.03ms, MSE =14.73), (F(1,18) = 32.03, p< 0.001. There was also a main effect of item type, reflecting that overall reaction time for old items (922.466ms, MSE = 14.00) was much slower than for new items (809.67ms, MSE =14.00), F(1,18) = 32.45, p < 0.001. A significant three-way interaction between polarity group, stimulation, and item type, F(1,18) = 32.45, p < 0.001 revealed that after anodal active stimulation participants were significantly faster (920.00ms, MSE = 28.58) responding to new faces than after sham stimulation (939.79ms, MSE =28.58), F(1,18) = 3.89, p<0.001.

Source memory accuracy

The source memory performance of participants was assessed with the mean accuracy on the memory judgements for old items correctly recognised with one or more source contexts for each trial (Figure 12). A between subject ANOVA of mean source accuracy for trials employing polarity group (Anodal, Cathodal), and stimulation (sham, active tDCS) yielded no significant main effects of current polarity group F(1,28)= 1.98, p=0.16, or stimulation condition *F(*1,18) = 2.87, p =0.09, or related interaction, *F(*1,18) =0.545, *p* =0.46. As in the

main experiment, within-group analyses employing the factor of stimulation were conducted separately for the Anodal and Cathodal groups. Analyses of effects of stimulation within groups showed that effect of active anodal tDCS on mean source accuracy (0.53, MSE= 0.02) did not differ significantly from sham stimulation (0.51, MSE = 0.02), $F(1,18) = 0.26$, $p = 0.61$. The effect of cathodal tDCS (0.57, MSE= 0.02) also was not significantly different from sham (0.53, MSE = 0.02), $F(1,18) = 2.05$, $p = 0.15$.

Discussion

The presented study demonstrates that retrieval of multisensory episodic contexts may be modulated by tDCS. In comparison to the sham stimulus condition, source memory retrieval performance increased following anodal stimulation over the left PPC, however no significant change was found for performance following cathodal stimulation. Most notably, the control experiment indicated that this increase in source memory performance was specifically modulated by the brain region underlying the left P3 site, as tDCS to the adjacent left Primary motor site did not lead to any significant change in source memory, though improvement in recognition potentially from adjacent PFC stimulation was found. These findings indicate that increased excitability of the PPC lead to improvements in retrieval of the multisensory contexts within trials. This relationship of the PPC activity was predicted by the earlier presented EEG findings of an association with this episodic retrieval, and it is supported by converging evidence which implicates the PPC in memory recollection. However, these findings contrast previous reports of absence of memory retrieval deficits in patients with PPC lesions (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Simons, Peers, Mazuz, Berryhill, & Olson, 2010). This discrepancy may be due in part to large-scale functional reorganization known to accompany long term brain damage (Price et al., 1999), which may be circumvented by temporary neuromodulation.

Modulation of memory performance by employing tDCS to the PPC was significant, however inhibitory cathodal stimulation proved less effective than excitatory anodal stimulation. Such a discrepancy in the effects of tDCS may be mediated by a difference between the densities of glutamatergic and GABAergic synaptic populations at the PPC site of stimulation, as

these populations differentially influence the physiological mechanisms which underlie the after effects of cathodal versus anodal tDCS. Individual differences in tissue density, as well as structural morphology between anodal and cathodal groups potentially may also lead to differences in the effects of tDCS (Paus et al., 1997), though follow up structural imaging would be necessary to identify such effects. Such individual differences, as well as individual differences that may exist in the baseline cognitive performance of participants which have been found to modulate the observed effects of tDCS (Tseng, 2012), may also have potentially played a role in the decreased effectiveness of cathodal stimulation.

Though these findings implicate activity from the PPC as subserving multimodal episodic retrieval, the use of tDCS constrains these findings to activity of this region quite broadly, and not with the precision of previous reported neuroimaging correlates. The spatial resolution of the region of stimulation under tDCS electrodes is quite course (reaching 25cm^2 surface area of scalp), and could not distinguish between the potential contributions of individual subregions of the PPC to memory retrieval. Predictions of independent influences of medial ventral PPC activity on recollection, and dorsal PPC activity on familiarity at retrieval (Vilberg & Rugg, 2008) could not be tested in the current study, as the region undergoing neuromodulation was not localized to either subregion. The behavioural effects we observe therefore may have resulted from changes induced throughout subregions of the PPC and cannot be specified to a single subregion. Likewise, the predictions that activity of the ventral and dorsal PPC subserve top-down initiated attentional retrieval processes, and bottom-up feature-driven attentional retrieval processes respectively (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008), are also not capable of being tested with this method, and the results may implicate activity of both regions. Methods of neuromodulation such as TMS, which employ focal sites of stimulation, may be capable of further investigating the contribution of PPC regions.

Previous research implicating the PPC in retrieval has been insufficient in specifying its role in binding of episodic features, due to the unimodal nature of episodic features they commonly link with measures of PPC activity (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Schloerscheidt & Rugg, 1997). The findings of our EEG investigation are among the

first to support an association of PPC activity with the integration of multi-sensory episodic features. Consequently the results of the current study are the first to indicate that successful multimodal episodic retrieval may not only be associated with increased PPC activity, but also that retrieval success is causally affected by enhancement of PPC activity. These findings may therefore offer more direct support for the role of PPC activity in episodic retrieval than previous literature provides, and suggest further work in elucidating the constraining factors of its involvement.

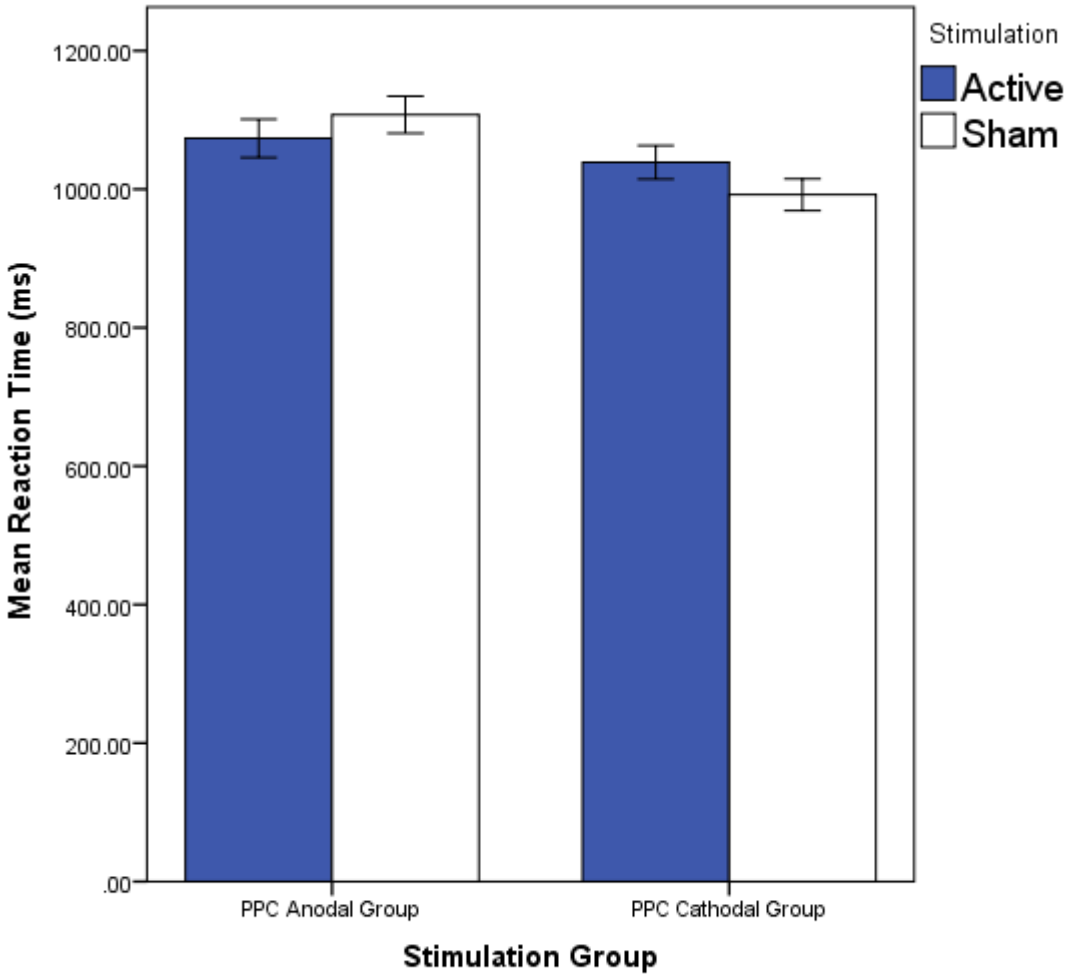

Figure 9. Mean RT for recognition test trials after PPC tDCS.

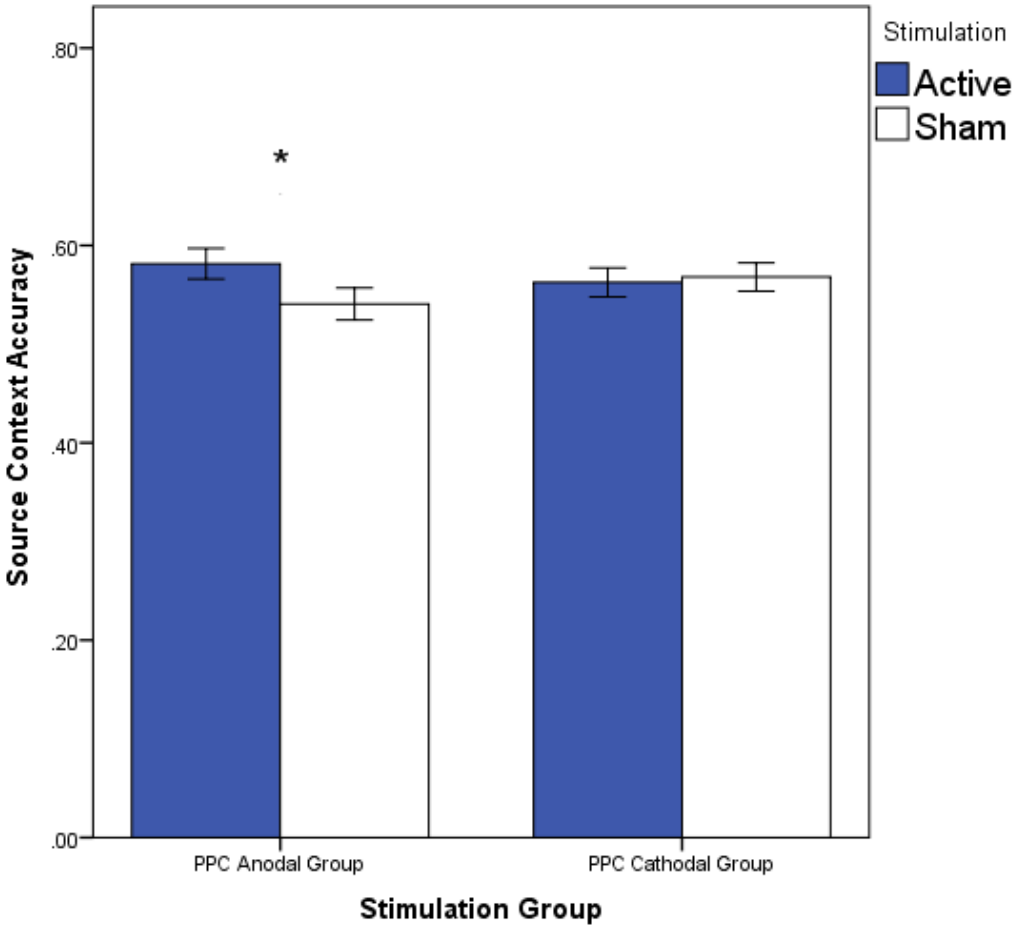

Figure 10. Source memory performance for PPC tDCS.

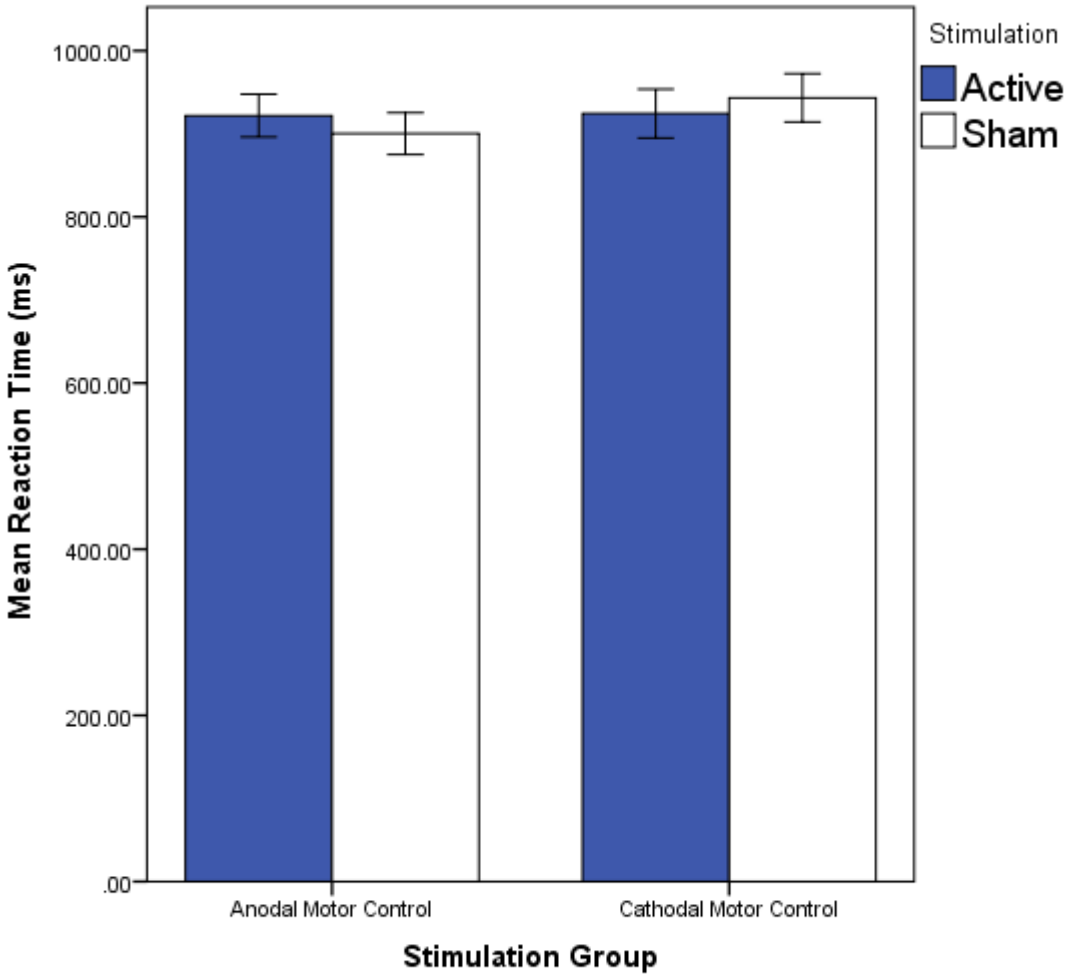

Figure 11. Mean RT for recognition test trials after M1 tDCS.

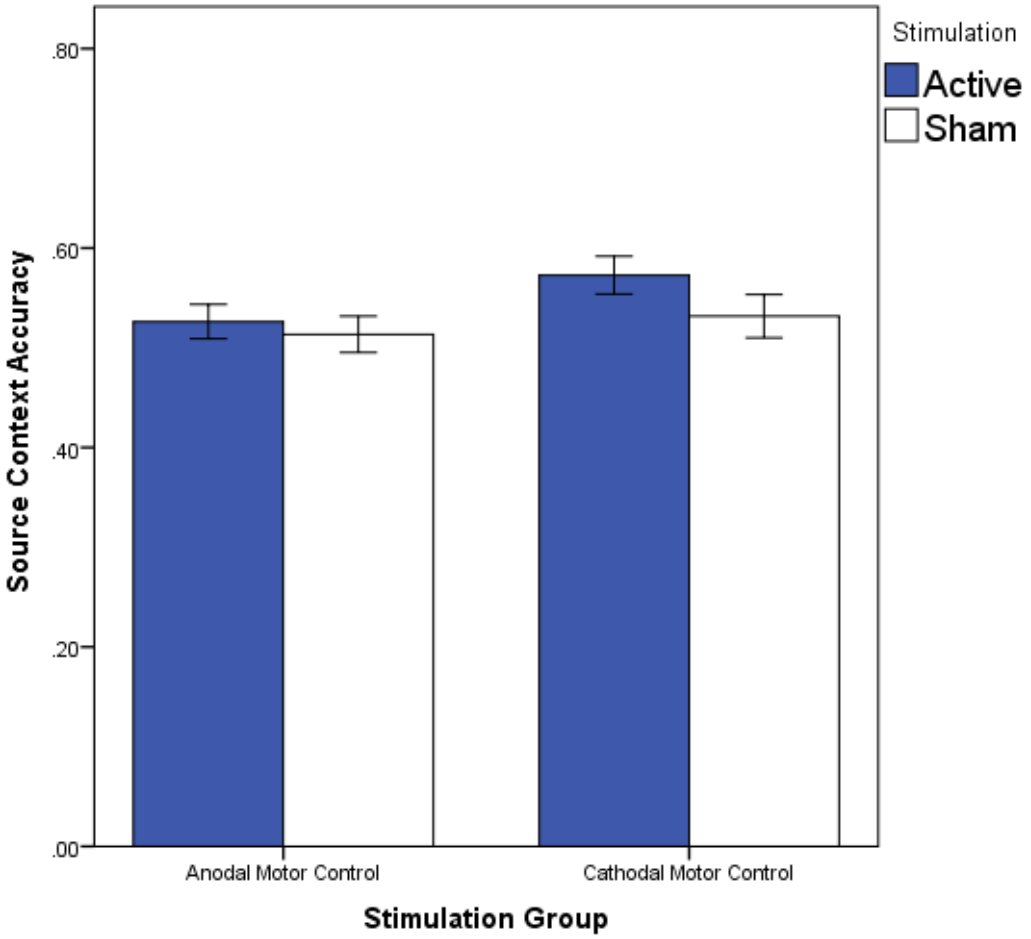

Figure 12. Source memory performance for M1 tDCS.

Chapter 6: Contribution of individual differences to posterior parietal neuromodulation of episodic retrieval

The use of neuromodulatory approaches such as external cortical stimulation for investigations of cognitive neuroscience has yielded a heterogeneity in the observed effects of induced plasticity. Although neuromodulation of motor cortex function has been pervasively examined for its behavioural effects (e.g. Rossini et al., 1994, 2015; Nitsche & Paulus, 2001), relatively few studies examining neuromodulation in other regions have presented effects that are consistent with those of motor plasticity. The challenge to demonstrate consistent behavioural effects is substantiated largely by the variability of the physiological effects of stimulation intensity and duration, as well as the directionality of stimulation effects, between different anatomical sites (Paus et al., 1997).

Further contributing to this challenge, even with consistent stimulation and structural parameters, there remains heterogeneity in the cognitive benefits of neuromodulation that individuals exhibit. Several participant characteristics have been identified as determinants of the differential effects of stimulation at a given cortical site, such as age, gender, or allelic expression (Ridding & Ziemann, 2010). Such factors may even modulate the effective direction of long term plasticity observed.

Further to this, any behavioural effects of plasticity are also subject to such determinants, and there have been findings of differential effects of neuromodulation due to pre-existing individual differences in cognitive performance. For example, working memory performance that was low at baseline was found to be more susceptible to the effects of neuromodulatory stimulation than when baseline performance was high (Tseng, 2012). Individual differences may reflect propensity for the “activity-selectivity” of tDCS to preferentially modulate a neuronal network that is currently activated, while not modulating separate neuronal networks that are inactive. The active and inactive networks can in fact overlap in space (e.g., in the same cortical column) such that tDCS activity-selectivity does not require physical separation and can represent a form of functional specificity. Neuromodulation may reflect changes in such salient processes, given that tDCS produces low-intensity “sub-

threshold" electric fields in the brain (Reato et al., 2010). Activity-selectivity differences are seen to arise at the cellular level, as direct current stimulation may enhance plasticity in a given synaptic pathway while applied at a preferential frequency of 0.1 Hz (Fritsch et al., 2010), or preferentially modulate the degree of potentiation in the activated pathway (Ranieri et al., 2012). At the systems level activity-selectivity may vary in preferential modulation of networks with heightened oscillatory activity (Reato et al., 2010) or in preferentially changing the developments within an active network during memory consolidation or synaptic downscaling (Reato et al., 2013). Generally variance in activity-selectivity is reflective of an ongoing network process becoming preferentially tuned to the influence of stimulation, in comparison to a host of other ongoing brain functions.

Krause et al. (2013) suggest that baseline cognitive variance may reflect that the balance between cortical excitation and inhibition (E/I balance) differs between individual brain areas as well as subjects, and may cause fundamentally different results of tDCS for an individual with high regional excitability, such that anodal tDCS will lead to overexcitation and non-optimal performance, whereas for an individual with lower excitation it may be more beneficial. The optimal excitability level would then be at the top of an inverted-U shaped function of excitation/inhibition and behaviour. In line with this hypothesis, researchers have now discovered that experimental populations can almost be split into responders and non-responders (López Alonso et al., 2014, Hamada et al., 2013). Such balances are likely reflected by neurotransmitters (i.e., the excessive release of glutamate, as overexcitation of the cortex, leads to excitotoxicity (Faden et al., 1989; Belousov, 2012). Excessive GABA inhibition, in contrast, prevents LTP and reduces neuronal output (Mcdonnell et al., 2007). Enhanced inhibition is therefore associated with higher network stability but also reduced cortical plasticity (Hess & Donoghue, 1996). Individual differences in pre-existing neurotransmitter levels and in cortical efficiency are also reflected in brain activity measured by fMRI, such that baseline levels of glutamate and GABA are associated with regional activity levels. Furthermore, task-dependent activity for several different cortical and subcortical regions is not only associated with glutamate levels within the given regions, but also in remote regions that are heavily connected. However, the direction of the relationship

between activity (low vs. high) and task demands is modulated by pre-existing glutamate levels (low vs. high) (Falkenberg et al., 2012).

Barriers to the consistency of tDCS effects are further found to arise from individual variations in the tissue morphology and functional localization within the brain (Sack et al., 2009; Krause & Kadosh, 2014). Head size and tissue thickness variation may lead to different current distributions and necessitate different current strengths to achieve the same current flow (Bikson et al., 2012), such that the stimulation may vary in focality, depending on where on the head the electrodes are placed. This will arise from the relationship between the orientation of neurons and the current flow applied, and how the current propagates along the tissue connections (Neuling et al., 2012). Morphological variations of cortical gyri and sulci also affect the pattern of the current flow, and consequently the same stimulation protocol can lead to large differences in the induced current and the resulting electric field (Datta et al., 2012; Truong et al., 2013). Thus the individual variation in the strength of the effects of electric field induction on neuronal activity and E/I balance can result in fundamental differences (Penton et al., 2018). Such observations have been made in experiments applying different intensities of current (Batsikadze et al., 2013), for which an intended excitation can flip to inhibition in some subjects but not in others. This in turn may negatively affect both physiological and behavioural effects.

The previous tDCS investigation implicated the PPC in binding of multimodal contexts within an episode through direct manipulation of PPC activity. Excitatory anodal stimulation to the left PPC was found selectively increase the richness of retrieval on a multimodal episodic memory task, however the observed effects of inhibitory cathodal stimulation were less robust. Given the substantial influence of individual factors to the variance in the effects of tDCS neuromodulation, the current study sought to investigate the contribution of pre-existing individual differences to the potentially attenuated observed effects of tDCS to the PPC. In order to account for the contribution of pre-existing individual states on the effects of stimulation, measures of baseline memory performance and fluid intelligence were obtained, and were used as determinants in an assessment of the effects of tDCS. It was predicted

that the individual variance in cognitive performance mediated the observed changes in the mean retrieval of source contexts caused by active stimulation.

Methods

Participants

Thirty participants (16 female, aged 19 to 39, mean = 23 years) completed the source memory task testing for multimodal retrieval as previously described in Chapter 5. Each was either paid at a rate of £7/hour, or received credit towards fulfilment of an experimental participation requirement for their course. All participants were right-handed, had no history of neurological or psychiatric disturbances, and did not meet any criteria of contraindications for safe use of tDCS (Nitsche, 2008). These criteria include history of drug abuse, fainting, or migraines, pregnancy, being a licensed HGV driver, or having any metallic implant in the neck, head or eye, or any other implanted electrical device. Participants provided written informed consent in a manner approved by the local department ethics. They were divided into two groups, with 15 participants in the anodal group, which received active anodal tDCS and sham stimulation, and 15 participants in the cathodal group, which received active cathodal tDCS and sham stimulation. From the anodal and cathodal group, a further 6 and 7 participants respectively completed the Cattel Culture Free Questionnaire for measuring Fluid intelligence.

Stimuli

Two hundred and fifty-six black and white photographs of faces (64 of famous celebrities, 192 from the Glasgow Unfamiliar Face Database (2010)) were used for the visual stimuli. The 64 famous and 64 nonfamous faces shown during study phases were matched in proportion on age, gender, and ethnicity, as were the 128 nonfamous faces only shown during test phases. Presentation order of faces was randomised between participants. Four audio recordings were used for auditory stimuli, one of each task question spoken by a male, and one of each task question spoken by a female.

Measure of fluid intelligence (CCF-IQ)

A sample of participants completed the paper based Cattell Culture Fair Intelligence Test Scale 2, form A (Institute for Personality and Ability Testing, 1973) on a separate day, which was used to assess potential contributions of individual differences in fluid intelligence to observed outcomes of tDCS. This IQ test has been widely used and has strong construct and concrete validity scores (.81 and .70, respectively), as well as test-retest, internal, and external reliability scores (.73, .76, and .67, respectively).

Procedure

Participants completed four blocks of the source memory task used in the previous studies and received active tDCS and sham tDCS on two blocks each, according to their current polarity group (anodal, cathodal). The source memory task consisted of two phases, a study and a test phase. On study phase trials participants were presented with a fixation cross at the centre of the screen for 1000ms. Then a famous personality or an unfamiliar face was presented either to the left or right side parallel to the fixation cross for 1sec, at which point participants were asked a 2000ms question from a male or female voice to perform one of two tasks via headphones. In the pleasantness task participants were asked to indicate if the face was pleasant or not. In the celebrity task they were asked to indicate if the face was of a celebrity or not. This was followed by a second screen with instructions to indicate on which side the face was shown, and a third to indicate the gender of the questioner, both preceded by presentation of a fixation cross for 100ms. They received on-screen instructions to indicate a choice by pressing the “c”, or the “m” key on the keyboard as quickly as possible up to a maximum of 2400ms. Each study phase lasted 32 trials and after they had been completed participants then received instructions to begin the test phase. Stimulation was administered during the study phase according to current polarity group (anodal, or cathodal).

In the test phase participants saw all faces from the study phase, as well as 32 new faces previously shown and were tested on their source memory for studied faces. On test trials participants first were presented with a fixation cross at the centre of the screen for 1000ms, followed by a face for another 1000ms, to which they were instructed on screen to indicate

whether it had been previously presented at study for a maximum of 2400ms. This was then followed by a second on-screen instruction to indicate which rating task they had completed for the given face, a third to indicate on which side the face was shown, and a fourth to indicated the gender of the questioner, each for a maximum of 2400ms, and preceded by presentation of a fixation cross for 100ms. For trials for which a new face stimulus was presented participants could press any key to respond for the last three indications. The test phase lasted 64 trials, and concluded the block, after which participants had the option to take a break before beginning the next block.

Following debriefing of the task participants were recruited to return on a different day for further psychometric testing, to which 13 participants agreed. Participants completed Cattel Culture Fair questionnaire for fluid intelligence at least 7 days following tDCS to ensure the termination of any potentially unknown lasting effects of PPC stimulation.

Transcranial direct current stimulation protocol

A CE-certified tDCS medical device was applied in this experiment with a small battery-driven constant current stimulator (BrainSTIM Transcranial Stimulator, EMS medical, UK). The stimulator consisted of a stimulator machine and a pair of conductive rubber electrodes (5cm X 5cm) inside two saline-soaked sponges that were secured on to the skin. One electrode was placed on the P3 site of the International 10-20 System for EEG electrode placement (Jasper, 1958) to stimulate the left posterior parietal cortex, and the other on the right cheek to serve as the reference (Jones & Berryhill, 2012; Tseng et al., 2012). In the active stimulation (on the P3 site) blocks, a constant current of 1.5 mA began at the onset of the study phase for each block and persisted for 4 minutes after the last study trial, lasting for a total of 10 min for each block. In the sham condition, the electrodes were also kept in place for the 10-minute interval but the current was applied only for the first 30 seconds. The fade-in and fade-out durations were 15 seconds for active and sham stimulation conditions. The stimulation alternated between active and sham stimulation type between blocks (two blocks each), with constant electrode placement throughout the experiment, according to the current polarity participant group.

Safety of tDCS depends on both current density and stimulation strength (Nitsche et al., 2003). The current density induced by the tDCS protocol in the present study was a maximum of 0.0428 mA/cm2, which was well below the safety value of 25 mA/cm2 (McCreery et al., 1990). In regard to the stimulation strength, the total charge was 0.0056 C/cm2. This value was also far below 216 C/cm2, which has been found to have no significant heating effect at the electrode site (Nitsche & Paulus, 2000), or evidence of any neuronal damage (Nitsche & Paulus, 2001; Nitsche et al., 2003). The tDCS protocol used in the current experiment was therefore in accordance with the literature and safe for the participants. Debriefing and questionnaires following the study verified that participants had not experienced any discomfort or irritation from tDCS. The experiments were approved by the local ethical committee.

Results

Recognition memory

Accuracy of participants for recognition test trials was investigated for old and new faces. A between subjects ANOVA was performed on the participant mean recognition scores with the factors of polarity group (Anodal, Cathodal), stimulation condition (sham, active tDCS), and item type (old, new). The main effect of stimulation was not significant $F(1,28)= 1.42$, $p=0.23$), nor was the main effect of polarity group ($F(1,28) = 1.39$, $p = 0.24$). There was a main effect of item type, reflecting that overall accuracy of (old) hits (0.804, SE=0.007) was much higher than for (new) correct rejections (0.760, SE = 0.007), $F(1,28) = 20.66$, $p < 0.001$. There was a significant three-way interaction between polarity group, stimulation, and item type, $F(1,28) = 7.90$, $p < 0.001$, and within subject analyses revealed that the after anodal active stimulation participants showed a significant lower rate of correct rejections $F(1,28) = 7.44$, $p<0.01$. There were however no significant interaction effects involving the old items, revealing no evidence that tDCS to the PPC modulated retrieval of old items.

Reaction time

The mean reaction times of participants on test trials was investigated for responses to old and new faces. A between subject ANOVA was performed with the factors of polarity group (Anodal, Cathodal), stimulation condition (sham, active tDCS), and item type (old, new). The

main effect of stimulation was not significant F(1,28)= 1.17, p = 0.28, however the main effect of polarity revealed that the Anodal group (1092.35ms, MSE = 14.15) had significantly slower reaction times than the Cathodal group (945.38ms, MSE =13.33), F(1,28) = 56.3, p< 0.001. There was also a main effect of item type, reflecting that overall reaction time for old items (1050.61ms, MSE = 13.75) was much slower than for new items (987.85ms, MSE =13.75), F(1,28) = 10.416, p = 0.001. A significant three-way interaction between polarity group, stimulation, and item type, F(1,28) = 7.90, p < 0.001 revealed that after anodal active stimulation participants were significantly faster (1039.81ms, MSE = 26.26) responding to old faces than after sham stimulation (1110.91ms, MSE =26.21), F(1,28) = 3.61, p=0.05. Conversely after anodal stimulation responses to new items were significantly faster 3 (1039.81ms, MSE = 26.26) compared to sham stimulation (1110.91ms, MSE = 25.77), F(1,28) = 67.32, p<0.001.

Contributions to source accuracy

In order to examine how individual variance in baseline cognitive functioning might mediate the effects of active tDCS on source retrieval, the mean accuracy of individual participants for source contexts of old items (source accuracy) after sham stimulation was used as a baseline for individuals' memory performance and compared to the source accuracy of individuals after active stimulation and to the individual CCFIQ scores. The mean (SE) CCF-IQ scores for anodal and cathodal groups were 36.67(1.9) and 33.5(3.9) respectively, which did not differ, F(1,11) = 0.659, p = 0.44. A hierarchical multiple regression was performed to assess whether the polarity of PPC stimulation (anodal or cathodal) was a significant determinant of source accuracy following active stimulation after accounting for baseline cognitive performance. Fluid intelligence score (CCIQ) and baseline source accuracy were entered as predictors of source accuracy following active stimulation in step 1, and polarity of stimulation was entered in step 2 of the regression. The full regression accounted for 79% of the variance in source accuracy following active stimulation, F(3,9) = 7.63, p=0.018, and the polarity of stimulation and baseline source accuracy were significant determinants over all. The variance accounted by baseline cognitive performance alone did not reach significance, but the inclusion of polarity of stimulation contributed an additional 26% of the

variance to the final regression, FΔ(1,9) = 7.47, p=0.03 (See table 1). The statistical significance for the contribution of the polarity of stimulation was however lost if it was included as a sole predictor of source accuracy following stimulation, F(1,12) = 0.17, p=0.69. Difference scores of individual changes in source memory performance were obtained by subtracting the individual baseline source accuracy means from the active stimulation means. These were used to assess to assess the covariation of the change in memory performance (Δsource accuracy) following active stimulation with individual baseline memory performance in each polarity group. In the anodal tDCS group Δsource accuracy was negatively correlated with baseline source accuracy, r = -0.66, p = 0.01, such that the positive Δsource accuracy after active stimulation was steadily reduced as baseline performance levels became higher, and Δsource accuracy became negative at the higher levels of baseline memory. The cathodal tDCS group however displayed a much weaker negative correlation of Δsource accuracy with baseline source accuracy, r =-0.159, p = 0.56, which trended a significant difference from the anodal group, z =-1.55, p = 0.056 (Figure 13).

Discussion

The findings from the current study exemplify that multimodal source memory performance can be decreased and increased by tDCS to the PPC. Modelling that accounted for the contribution of individual baseline memory performance revealed that active stimulation to the PPC significantly influenced subsequent retrieval of multimodal source contexts. Furthermore the influence of individual differences in baseline performance was found to mediate the positive or negative direction of the change in performance induced by tDCS. Changes in source accuracy following anodal stimulation to the PPC were associated with positive increases for individuals with lower memory performance baselines but were increasingly negative for participants with high memory performance at baseline. These findings reveal a function of the causal modulation of memory retrieval by PPC activity that is dependent baseline cognitive performance, unique to this study. Most notably, they further delineate a contribution of PPC activity that is independent of recognition memory performance, and specific to the objective retrieval of multimodal source contexts, which we found to be integrated across a graded continuum.

Several studies using tDCS have shown that baseline performance can predict the magnitude of change in performance following stimulation (Tseng et al., 2012, 2018; Hsu et al., 2014, 2016; Krause & Cohen Kadosh, 2014; Benwell et al., 2015; Fertonani & Miniussi, 2017; Penton et al., 2018). Other studies that also applied tDCS over the PPC have shown, despite identical montages, that the positive effects of tDCS on cognitive functions such as WM and spatial attention can vary depending on the participants' current cognitive context and task set (Tseng et al., 2012; Hsu et al., 2014; Wu et al., 2014, 2016). Given the state-dependence of brain stimulation effects (Silvanto et al., 2008) it is likely that differential effects in high vs. low performers may also be linked to differences in the state-dependent outcomes of stimulation effects (potentially derived from separate brain networks recruited at task). It has been suggested that this may be due to differential recruitment of brain networks/brain states in high and low performers (Tseng et al., 2012; Krause and Cohen Kadosh, 2014). Individual baseline performance may also reflect differences in the state-dependency/signal-to-noise ratio, as it is proposed that the relative balance between task-relevant ("signal") and irrelevant ("noise") neurons at baseline determines tDCS outcomes (Silvanto et al., 2007, 2008; Miniussi et al., 2010, 2013; Ruzzoli et al., 2010; Benwell et al., 2015). Simultaneously boosting both subgroups of neurons by anodal stimulation, for example, would cause these two subgroups of neurons to compete with each other through mutual inhibition and lead to poor performance.

An alternative pathway for such activity-selectivity is that anodal stimulation may keep active neurons from declining, thus leading to poor performance. This behaviour was evident in a L-dopa study by Monte-Silva et al. (2010), where optimal cognitive functions were only observed with medium dosage of L-dopa. Increasing the L-dopa actually resulted in a decline in cognitive functioning, suggesting that either extremely high or low neuronal activity is associated with poor performance, which for some individuals would also result from anodal or cathodal tDCS.

The relationship revealed by the current study between the effects of stimulation to the PPC on source memory performance, and how these effects are mediated by baseline cognition, accounts for both the predominant positive and infrequent negative changes in source

accuracy due to increased PPC activity caused by excitatory anodal stimulation. In contrast, cathodal stimulation revealed a weak mediation of its effects by baseline cognition, and this relationship trend conversely accounts for both the (majority) negative and positive changes in source accuracy due to decreased PPC activity. Although the relationship between the effects of source memory performance and baseline cognition observed in this context are specified to effects of manipulations of tDCS, it is possible for such a relationship to be extended to measures in other studies which might similarly examine modulations of PPC activity or function in source memory. It remains a potential for further examinations of the richness of episodic retrieval to account for mediation of baseline cognition, in order to provide a more robust account of observed effects that might otherwise be small because of individual differences.

The significant influence of active tDCS to the PPC on source accuracy corroborates the findings from our previously presented studies that associated increase in PPC activity with the increased richness of multimodal contexts during episodic retrieval, and enhanced source accuracy performance following excitatory anodal stimulation of the PPC. This finding consequently adds further support for the proposed role of the PPC as an integrating hub that is responsible for binding multimodal contexts of episodes during retrieval, which has been suggested by imaging findings associating it with recollective detail, vividness, and richness (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Vilberg & Rugg, 2008; Ranganath & Ritchey, 2012; Shannon & Buckner, 2004; Kuhl and Chun, 2014; Rissman, Chow, Reggente, & Wagner, 2016), as well as more recently neuromodulation findings of recollection confidence, and cross-modality, and recall (Yazar, Bergstrom, & Simons, 2017; Yazar, Bergstrom, and Simons; 2014, Chen et al 2016; Pergolizzi and Chua, 2015; Jones, Gozenman, & Berryhill, 2014).

The mediation of baseline cognition for tDCS also provide a function that accounts for the discrepancies in the patient lesion literature which largely support the absence of objective memory retrieval deficits following organic PPC lesions (Ally, Simons, McKeever, Peers, & Budson, 2008; Haramati, Soroker, Dudai, & Levy, 2008; Hower, Wixted, Berryhill, & Olson, 2014; Simons, Peers, Mazuz, Berryhill, & Olson, 2010). It is possible that individual

differences in patients' premorbid memory functions may similarly mediate the impact of decreased functionality of the PPC due to insult, such that effects on memory performance are attenuated at higher levels of premorbid functioning. Inclusion of such measures in future studies of PPC patients may therefore reveal similar mediated influences on memory retrieval.

Table 1.

Fluid Intelligence, baseline memory performance, and stimulation polarity as predictors of source accuracy following stimulation

	Model 1				Model 2			
	B	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Constant	0.089	0.2		0.670	-0.020	0.149		0.900
CCIQ	0.004	0.005	0.233	0.399	0.000	0.000	0.000	0.000
Baseline Source Accuracy	0.615	0.241	0.664	0.038	0.930	0.208	1.004	0.004
Stimulation Polarity					0.132	0.048	0.635	0.034
R^2	0.534				0.792			
ΔR^2	0.534				0.259			
F for ΔR^2	4.005			0.069	7.467			0.034
F	4.005			.069	7.626			0.018

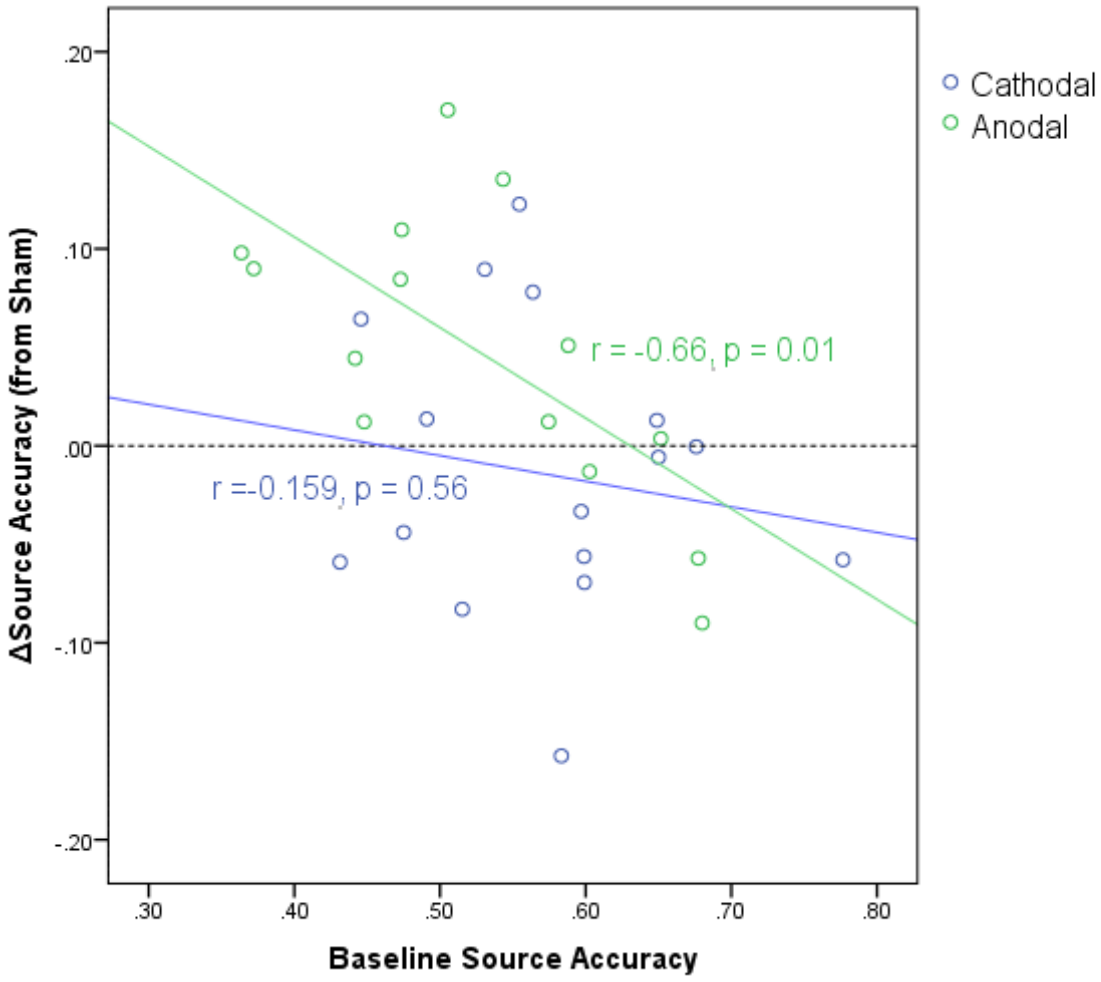

Figure 13. Correlation between baseline source accuracy, and the change in source accuracy performance after active cathodal and anodal tDCS to the PPC

7. General Discussion

In two ERP studies and association the Old/New parietal ERP component was made with increased success in retrieving multimodal sources in the episodic memory task. This supported predictions based on previous literature that PPC activity was associated with multimodal episodic retrieval. The ERP results indicated that the contextual richness of episodic retrieval increased with the strength of an early Old/New effect arising from posterior parietal sites, and these changes differed from those underlying frontal Old/New effects observed in a similar time window not only in terms of greater magnitude, but also in sensitivity to increased source retrieval. The subsequent two investigations demonstrated a causal role of the PPC during episodic retrieval, and that retrieval of multisensory episodic contexts was modulated by tDCS. In comparison to the sham stimulus condition, source memory retrieval performance increased following anodal stimulation over the left PPC, however no significant change was found for performance following cathodal stimulation. Further investigation of individual differences in baseline performance was found to mediate the positive or negative direction of the change in performance induced by tDCS. This manifested as changes in source accuracy following anodal stimulation to the PPC being associated with positive increases for individuals with lower memory performance baselines but being increasingly negative for participants with high memory performance at baseline.

Literature implicating the role of the PPC in episodic retrieval have been heterogeneous. Despite the considerable convergence on its impact on memory retrieval measures, the indicators of this have been quite varied across studies, and this has made numerous conceptions of the precise retrieval processes being driven by the PPC potentially capable of being supported by the research (Shimamura, 2011). Hitherto more constrained evidence from neuropsychological literature has been sparse, and has yet to yield less disputable findings that support the proposed retrieval integration processes (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Simons, Peers, Mazuz, Berryhill, & Olson 2010).

Parietal lesion patients exhibit subtle deficits in retrieval-related processes, such as retrieval confidence, and these present a challenge to isolate, amidst the host of other comorbid

perceptual and cognitive impairments common to this population. Insults which induce lesions to the PPC, such as stroke, rarely spare neighbouring tissues, and other related cognitive functions are often compromised (Haramati, Soroker, Dudai, & Levy, 2008). As a consequence such retrieval deficits rarely occur in the context of otherwise normal cognitive functioning. This further limits the potential of these findings to demonstrate function of the PPC in the normal brain.

Moreover, of the select findings of lesion deficits in retrieval success, they have not demonstrated the causal role in retrieval of the rich multi-modal episodic features proposed for the PPC. Such subtle retrieval deficits resulting from PPC impairment may not be detected due to the dense connectivity the PPC shares directly with functional regions throughout the brain, and with other dense hubs of connectivity (Bullmore, 2009). This connectivity may facilitate its regional losses in function being offloaded across many interconnected sites, as such long term brain damage is found to lead to local and even large-scale functional reorganization (Price et al., 1999). Lesion patient studies therefore may not be indicative of normal contributions of PPC function in episodic retrieval (Schoo et al., 2001).

The use of directed plasticity however, such as external stimulation, within the normally functioning brain may be essential to demonstrating the PPC's role in this manner. A non-invasive method of external stimulation for inducing sustained disruption of cortical activity is transcranial magnetic stimulation (TMS). When applied at a specific frequency of stimulation, TMS can cause temporary disruption of activity for a targeted site (Rossini et al., 1994, 2015). These temporary "virtual lesions" can present an improvement over patient models of cortical contributions to cognitive function, in that they can be readily applied in healthy brains, and participants may be tested for effects immediately following TMS, before widespread cortical reorganization may occur (O'Shea et al., 2007; Robertson et al., 2003).

The use of neuromodulatory approaches such as external cortical stimulation for investigations of cognitive neuroscience has yielded a heterogeneity in the observed effects of induced plasticity. Although neuromodulation of motor cortex function has been

pervasively examined for its behavioural effects (e.g. Rossini et al., 1994, 2015; Nitsche & Paulus, 2001), relatively few studies examining neuromodulation in other regions have presented effects that are consistent with those of motor plasticity. The challenge to demonstrate consistent behavioural effects is substantiated largely by the variability of the physiological effects of stimulation intensity and duration, as well as the directionality of stimulation effects, between different anatomical sites (Paus et al., 1997).

Further contributing to this challenge, even with consistent stimulation and structural parameters, there remains heterogeneity in the cognitive benefits of neuromodulation that individuals exhibit. Several participant characteristics have been identified as determinants of the differential effects of stimulation at a given cortical site, such as age, gender, or allelic expression (Ridding & Ziemann, 2010). Such factors may even modulate the effective direction of long term plasticity observed. Further to this, any behavioural effects of plasticity are also subject to such determinants, and there have been findings of differential effects of neuromodulation due to pre-existing individual differences in cognitive performance. Working memory performance that was low at baseline was found to be more susceptible to the effects of neuromodulatory stimulation than when baseline performance was high (Tseng, 2012). Challenges to the consistency of neuromodulatory effects are even found to arise from variability in the structural and functional localization of a chosen anatomical site for neuromodulation across participants (Sack et al., 2009).

Much of the findings from the research presented have supported the converging evidence that the PPC serves a functional role in episodic retrieval, such as the finding increased activation of the PPC at retrieval was associated with greater retrieval of episodic features, and that increased stimulation of this activation lead to enhanced episodic retrieval. We also found that parietal ERPs were associated with the multimodality of retrieved episodes. Surprisingly, our investigation is the first to examine the PPC's role within a rich episodic context with multi-sensory retrieval, which provides a more complete picture of how the PPC is involved with the integration of different features that is commonly experienced during episodic retrieval. Quite novel to this investigation, employing both neurophysiological

measures and neuromodulation within an episodic retrieval task affords a causal relationship to be inferred from the link between PPC activation and episodic retrieval.

The combination of methods to examine episodic retrieval provide an opportunity to refine the nature of the proposed integration process which may not be possible to demonstrate alone. The findings of performance enhancements following excitatory stimulation are supported by indications that the same enhancements were coupled with increased activity, as well as vice versa. Although we don't find significant differences in performance following inhibitory neuromodulation, this may reflect limitations of this method in enhancing the PPC's role in task performance, or even differential effects of this method on PPC function due to pre-existing individual differences, which we found some evidence were involved.

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